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(54) Title: TELOMERASE INHIBITOR

(57) Abstract: The present invention provides a telomerase inhibitor containing as an active ingredient a compound which has the 4-oxo-2-thioxoimidazolidine skeleton and which has telomerase inhibitory activity.



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Telomerase Inhibitor

CROSS-REFERENCES TO RELATED APPLICATIONS

[01] This application claims the benefit of U.S. Provisional Application No. 60/259,124, filed December 30, 2001, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[02] The present invention relates to telomerase inhibitors and antitumor agents containing a 4-oxo-2-thioxoimidazolidine derivative (i.e., thiohydantoin derivative) or a pharmaceutically acceptable salt thereof. Such telomerase inhibitors and antitumor agents can be used for the treatment of diseases related to telomerase activity, e.g., malignant tumors. The present invention also relates to thiohydantoin derivatives or pharmaceutically acceptable salts thereof.

BACKGROUND OF THE INVENTION

[03] Telomeres are present at the termini of eukaryotic chromosomes and are believed to be essential to the stabilization of chromosomes. In humans, the telomere sequence consists of repetitions of TTAGGG from the 5' end. Although there are few exceptions, telomeres in normal cells usually undergo a gradual reduction in length as the cell divides. The cell becomes an aged cell (M1 phase) and ceases to divide when the telomeres are shortened to a certain length. However, when there is mutation in a cancer suppressor gene, e.g., p53 gene, the cell keeps dividing until the telomeres are reduced to extremely short lengths resulting in instability of the chromosomes and the cell death (M2 phase). See, for example, *Proc. Natl. Acad. Sci. USA*, vol. 89, pp. 10114-10118 (1992) and *Trends in Cell Biology*, vol. 5, pp. 293-297 (1995).

[04] In addition, it is believed that 80% or more cancer cells express an enzyme called telomerase, which extends telomeres. *Journal of the NCI*, vol. 87, pp. 884-894 (1995). Telomerase is a reverse transcription enzyme that extends telomeres using RNA as a template. Telomerase is composed of a template RNA (hTR) and a catalytic subunit protein (hTERT). It is believed that the telomerase in cancer cells suppresses or prevents shortening of the telomeres, thereby rendering the cancer cells immortal, i.e., indefinitely growing by maintaining the length of the telomeres. This theory, often referred to as the "telomere hypothesis", was proposed in 1992 by Cal Harley et al. *Proc. Natl. Acad. Sci. USA*, vol. 89,

pp. 10114-10118 (1992). The telomere hypothesis has been supported experimentally. For example, administration of an antisense agent against hTR results in telomere reduction and cancer cell death. *Science*, vol. 269, pp. 1236-1240 (1995). In addition, expression of a dominant-negative mutant hTERT which inhibits wild type telomerase also results in telomere reduction and cancer cell death. *Genes & Development*, vol. 13, pp. 2388-2399 (1999) and *Nature Medicine*, vol. 5, pp. 1164-1170 (1999). Therefore, it is believed that compounds that specifically inhibit telomerase may be used as a new type of antitumor agents by inducing a telomere reduction and limiting the life span of cancer cells. Such compounds are expected to be low-toxicity antitumor agents with minimal affect on normal tissues, because the telomerase is expressed only in cancer cells with few exceptions, such as reproductive cells, etc.

[05] Examples of known low molecular weight compounds that inhibit telomerase in vitro include: nucleic acid analogs, e.g., AZTTP, ddGTP [*Mol. Cell. Biol.*, vol. 16, pp. 53-65 (1996)], and 7-deaza-dGTP [*Biochemistry*, vol. 35, pp. 15611-15617 (1996)]; hetero 5-membered ring fused pyridine derivatives [U.S. Patent Nos. 5,656,638 and 5,760,062]; benzothiophene derivatives [U.S. Patent No. 5,703,116]; pyridine derivatives [U.S. Patent Nos. 5,767,278 and 5,770,613]; anthraquinones [*J. Med. Chem.*, vol. 40, pp. 2113-2116 (1997) and Japanese Laid-Open Patent Publication No. 11-35457]; triazine derivatives [Japanese Laid-Open Patent Publication No. 11-60573]; and phenylisothiazole derivatives [WO99/08679]. In addition, telomerase inhibitory activity and reduction of telomere in cancer cells have been associated with catechins, which are present in green teas. *Biochem. Biophys. Res. Commun.*, vol. 249, pp. 391-396 (1998). Other reported telomerase inhibitors include TMPyP4, a porphyrin having positive charge. *J. Am. Chem. Soc.*, vol. 120, pp. 3261-3262 (1998) and WO98/33503.

[06] Thiohydantoin derivatives have been reported to have a variety of pharmaceutical activities, such as anti-allergic and anti-inflammatory [e.g., WO97/28147 and Japanese Laid-Open Patent Publication No. 2-62864]; anti-ulcer [Japanese Laid-Open Patent Publication No. 8-225537]; blood sugar level reduction [*Arzneim. Forsch.*, vol. 50, pp. 626-630 (2000)]; aldose reductase inhibition [*Farmaco*, vol. 49, pp. 443-447 (1994)]; and the like. In addition, thiohydantoin derivatives are known to be effective in preventing and have therapeutic effects on tissue damage associated with lipid peroxide [Japanese Laid-Open Patent Publication No. 5-331148]. Moreover, thiohydantoin derivatives are reported to be useful in optic materials [e.g., Japanese Laid-Open Patent Publication No. 6-128234].

However, no telomerase inhibiting activity of thiohydantoin derivatives has been reported to date.

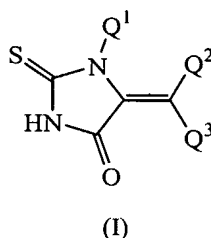
BRIEF SUMMARY OF THE INVENTION

[07] Some aspects of the present invention provide telomerase inhibitors, antitumor
5 agents, and novel thiohydantoin derivatives having excellent telomerase inhibitory activity and antitumor activity.

[08] In one aspect, the present invention provides a compound having a telomerase inhibitory activity, wherein the compound comprises a 4-oxo-2-thioxoimidazolidine skeleton.

[09] In another aspect, the present invention provides an antitumor agent
10 comprising as an active ingredient a compound having a 4-oxo-2-thioxoimidazolidine skeleton and having a telomerase inhibitory activity.

[10] Yet another aspect of the present invention provides a telomerase inhibitor comprising a compound of the formula:



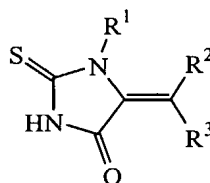
15 or a pharmaceutically acceptable salt thereof,
wherein

[11] Q¹ is hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted
20 aralkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted arylalkenyl, substituted or unsubstituted heteroarylalkenyl, substituted or unsubstituted arylalkynyl, substituted or unsubstituted heteroarylalkynyl, substituted or unsubstituted lower alkanoyl, substituted or unsubstituted lower alkenoyl, substituted or unsubstituted lower alkynoyl, substituted or unsubstituted arylalkanoyl, substituted or unsubstituted heteroarylalkanoyl,
25 substituted or unsubstituted arylalkenoyl, substituted or unsubstituted heteroarylalkenoyl, substituted or unsubstituted arylalkynoyl, or substituted or unsubstituted heteroarylalkynoyl;

[12] Q² and Q³ are different, and one of them is hydrogen, and the other is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[13] Still another aspect of the present invention provides an antitumor agent comprising the Compound of Formula I above or a pharmaceutically acceptable salt thereof, as an active ingredient.

[14] Yet another aspect of the present invention provides a compound of the
5 formula:

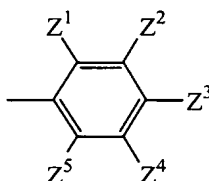


(Ia)

wherein

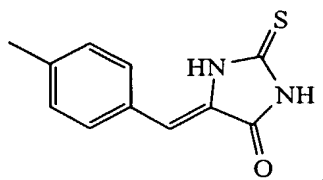
[15] R¹ is hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted arylalkenyl, substituted or unsubstituted heteroarylalkenyl, substituted or unsubstituted arylalkynyl, or substituted or unsubstituted heteroarylalkynyl;

[16] one of R² and R³ is hydrogen, and the other is a moiety of the formula:



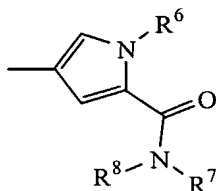
[wherein

[17] each Z¹ to Z⁵ is independently hydrogen, substituted or unsubstituted lower alkyl, unsubstituted lower alkoxy having no asymmetric carbon atom, substituted lower alkoxy, unsubstituted lower alkylthio having no asymmetric carbon atom, substituted lower alkylthio, NR⁴R⁵ (wherein R⁴ and R⁵ are the same or different, and each represents hydrogen, lower alkyl, lower alkenyl, lower alkynyl, lower alkanoyl, aroyl, heteroaroyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroarylalkyl, or a moiety of the formula



or R^4 and R^5 together with the nitrogen atom to which they are attached to form a substituted or unsubstituted heterocyclic group), nitro, cyano, aryl, heteroaryl, aryloxy, heteroaryloxy, aralkyloxy, heteroarylalkyloxy or halogen, or two of the substituents Z^1 to Z^5 that are attached to the adjacent carbon atoms on the benzene ring together form a moiety of the formula $-O-(CH_2)_n-O-$ (wherein n represents an integer of 1 or 2)],

[18] substituted or unsubstituted naphthyl, substituted or unsubstituted heteroaryl, or a moiety of the formula:

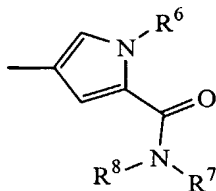


wherein

[19] R^6 has the same meaning as the aforementioned R^1 ;

[20] each of R^7 and R^8 is independently hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroarylalkyl, or R^7 and R^8 together with the nitrogen atom to which they are attached to form a substituted or unsubstituted heterocyclic group;

[21] with the proviso that when one of R^2 and R^3 is hydrogen, and the other is not



wherein

[22] R^6 , R^7 and R^8 are those defined above, R^1 is the above-mentioned substituent other than hydrogen and substituted or unsubstituted methyl.

[23] Still another aspect of the present invention provides a telomerase inhibitor comprising the Compound of Formula Ia above or a pharmaceutically acceptable salt thereof, as an active ingredient.

[24] Another aspect of the present invention provides an antitumor agent comprising the Compound of Formula Ia above or a pharmaceutically acceptable salt thereof, as an active ingredient.

[25] Yet another aspect of the present invention provides a medicament comprising the Compound of Formula Ia above or a pharmaceutically acceptable salt thereof, as an active ingredient.

[26] The Compound having a 4-oxo-2-thioxoimidazolidine skeleton and having
5 telomerase inhibitory activity according to the present invention is preferably the Compound of Formula I above, and more preferably the Compound of Formula Ia above. However, it should be appreciated that the compounds of the present invention are not limited to such.

DETAILED DESCRIPTION

[27] Hereinafter, Compound of Formula (I) or (Ia) may be denoted as Compound
10 (I) or (Ia), respectively. Similar notations apply to compounds of formulae with other numerals.

[28] Respective groups in formula (I) are subject to the following definitions.

[29] "Lower alkyl" refers to a linear or branched saturated monovalent hydrocarbon moiety of 1 to 6 carbon atoms, e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-
15 butyl, isobutyl, pentyl, and hexyl.

[30] "Lower alkenyl" refers to a linear or branched monovalent hydrocarbon moiety of 2 to 10 carbon atoms having one or more carbon-carbon double bonds, e.g., vinyl, propenyl, methacryl, prenyl, butenyl, pentenyl, hexenyl, and geranyl.

[31] "Lower alkynyl" refers to a linear or branched monovalent hydrocarbon
20 moiety of 2 to 6 carbon atoms having one or more carbon-carbon triple bonds, e.g., ethynyl, propynyl, butynyl, pentynyl, and hexynyl.

[32] "Aryl" refers to monocyclic, bicyclic, or tricyclic aromatic rings, e.g., phenyl, naphthyl, anthryl, and the like.

[33] "Heteroaryl" refers to monocyclic, bicyclic, or tricyclic aromatic heterocyclic
25 rings, e.g., pyridyl, thienyl, furyl, pyrrolyl, imidazolyl, pyrimidinyl, oxazolyl, thiazolyl, pyrazolyl, quinolyl, quinoxalynyl, quinazolyl, benzopyranyl, benzothienyl, benzofuryl, indolyl, benzimidazolyl, benzothiazolyl, indazolyl, benzodioxanyl, benzoxazolyl, and the like.

[34] "Alkylene," "alkenylene" and "alkynylene" refer to the corresponding divalent
30 form of lower alkyl, lower alkenyl and lower alkynyl, respectively.

[35] "Aalkyl" or "heteroarylalkyl" refers to a moiety of the formula $-R'-R''$, where R' is alkylene and R'' is aryl or heteroaryl, respectively, as defined herein.

[36] "Arylalkenyl" or "heteroarylalkenyl" refers to a moiety of the formula $-R'-R''$, where R' is alkenylene and R'' is aryl or heteroaryl, respectively, as defined herein.

[37] "Alkynylene" or "heteroarylalkynyl" refers to a moiety of the formula $-R'-R''$, where R' is alkynylene and R'' is aryl or heteroaryl, respectively, as defined herein.

5 [38] Substituted aryl, substituted heteroaryl, substituted aralkyl, substituted heteroarylalkyl, substituted arylalkenyl, substituted heteroarylalkenyl, substituted arylalkynyl, substituted heteroarylalkynyl, substituted arylalkanoyl, substituted heteroarylalkanoyl, substituted arylalkenoyl, substituted heteroarylalkenoyl, substituted arylalkynoyl, and substituted heteroarylalkynoyl may include one or more, up to the substitutable number of, substituents; preferably 1 to 5 substituents. Examples of such substituents include:

[39] substituted or unsubstituted lower alkyl;

[40] substituted or unsubstituted lower alkenyl;

[41] substituted or unsubstituted lower alkynyl;

[42] hydroxy;

15 [43] substituted or unsubstituted lower alkoxy;

[44] aryl;

[45] aryloxy;

[46] heteroaryloxy;

[47] aralkyl;

20 [48] substituted aralkyl {where substituent(s) for the aralkyl may be the same or different, and include one or more, up to the substitutable number of, substituents; preferably 1 to 5 substituents, such as lower alkyl, trifluoromethyl, hydroxy, lower alkoxy, trifluoromethoxy, mercapto, lower alkylthio, aryl, NR^9R^{10} (where R^9 and R^{10} may be the same or different and represent hydrogen or lower alkyl), nitro, cyano, CO_2R^{11} (where R^{11} represents hydrogen or lower alkyl), $CONR^{12}R^{13}$ [where R^{12} and R^{13} may be the same or different and represent hydrogen, lower alkyl, aryl, heteroaryl, aralkyl, or heteroarylalkyl; or alternatively, R^{12} and R^{13} together with the nitrogen atom to which they are attached to form a substituted or unsubstituted heterocyclic group], arylsulfonylmethyl, methylenedioxy, propylenedioxy, and halogen};

30 [49] aralkyloxy;

[50] heteroarylalkyl;

[51] substituted heteroarylalkyl [where substituent(s) for the heteroarylalkyl may be the same or different, and include one or more, up to the substitutable number of, substituents; preferably 1 to 5 substituents, such as lower alkyl, trifluoromethyl, hydroxy,

lower alkoxy, trifluoromethoxy, mercapto, lower alkylthio, aryl, $\text{NR}^{9a}\text{R}^{10a}$ (where R^{9a} and R^{10a} are same as R^9 and R^{10} , respectively), nitro, cyano, $\text{CO}_2\text{R}^{11a}$ (where R^{11a} is same as R^{11}), $\text{CONR}^{12a}\text{R}^{13a}$ (where R^{12a} and R^{13a} are same as R^{12} and R^{13} , respectively), arylsulfonylmethyl, methylenedioxy, propylenedioxy, and halogen];

5 [52] heteroarylalkyloxy;

[53] arylalkenyl;

[54] substituted arylalkenyl [where substituent(s) for the arylalkenyl may be the same or different, and include one or more, up to the substitutable number of, substituents; preferably 1 to 5 substituents, such as lower alkyl, trifluoromethyl, hydroxy, lower alkoxy,

10 trifluoromethoxy, mercapto, lower alkylthio, aryl, $\text{NR}^{9A}\text{R}^{10A}$ (where R^{9A} and R^{10A} are same as R^9 and R^{10} , respectively), nitro, cyano, $\text{CO}_2\text{R}^{11A}$ (where R^{11A} is same as R^{11}), $\text{CONR}^{12A}\text{R}^{13A}$ (where R^{12A} and R^{13A} are same as R^{12} and R^{13} , respectively), arylsulfonylmethyl, methylenedioxy, propylenedioxy, and halogen];

[55] heteroarylalkenyl;

15 [56] substituted heteroarylalkenyl [where substituent(s) for the heteroarylalkenyl may be the same or different, and include one or more, up to the substitutable number of, substituents; preferably 1 to 5 substituents, such as lower alkyl, trifluoromethyl, hydroxy, lower alkoxy, trifluoromethoxy, mercapto, lower alkylthio, aryl, $\text{NR}^{9Aa}\text{R}^{10Aa}$ (where R^{9Aa} and R^{10Aa} are same as R^9 and R^{10} , respectively), nitro, cyano, $\text{CO}_2\text{R}^{11Aa}$ (where R^{11Aa} is same as R^{11}), $\text{CONR}^{12Aa}\text{R}^{13Aa}$ (where R^{12Aa} and R^{13Aa} are same as R^{12} and R^{13} , respectively), arylsulfonylmethyl, methylenedioxy, propylenedioxy, and halogen];

[57] arylalkynyl;

[58] substituted arylalkynyl [where substituent(s) for the arylalkynyl may be the same or different, and include one or more, up to the substitutable number of, substituents;

25 preferably 1 to 5 substituents, such as lower alkyl, trifluoromethyl, hydroxy, lower alkoxy, trifluoromethoxy, mercapto, lower alkylthio, aryl, $\text{NR}^{9B}\text{R}^{10B}$ (where R^{9B} and R^{10B} are same as R^9 and R^{10} , respectively), nitro, cyano, $\text{CO}_2\text{R}^{11B}$ (where R^{11B} is same as R^{11}), $\text{CONR}^{12B}\text{R}^{13B}$ (where R^{12B} and R^{13B} are same as R^{12} and R^{13} , respectively), arylsulfonylmethyl, methylenedioxy, propylenedioxy, and halogen];

30 [59] heteroarylalkynyl;

[60] substituted heteroarylalkynyl [where substituent(s) for the heteroarylalkynyl may be the same or different, and include one or more, up to the substitutable number of, substituents; preferably 1 to 5 substituents, such as lower alkyl, trifluoromethyl, hydroxy, lower alkoxy, trifluoromethoxy, mercapto, lower alkylthio, aryl, $\text{NR}^{9Ba}\text{R}^{10Ba}$ (where R^{9Ba} and

R^{10Ba} are same as R^9 and R^{10} , respectively), nitro, cyano, CO_2R^{11Ba} (where R^{11Ba} is same as R^{11}), $CONR^{12Ba}R^{13Ba}$ (where R^{12Ba} and R^{13Ba} are same as R^{12} and R^{13} , respectively), arylsulfonylmethyl, methylenedioxy, propylenedioxy, and halogen];

[61] lower alkanoyl;

5 [62] lower alkanoyloxy;

[63] mercapto;

[64] substituted or unsubstituted lower alkylthio;

[65] heteroaryl;

[66] $NR^{14}R^{15}$ {where each R^{14} and R^{15} is independently hydrogen, lower alkyl,
 10 lower alkanoyl, aroyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, substituted aryl [where substituent(s) for the aryl include one or more, up to the substitutable number of, substituents; preferably 1 to 5 substituents, such as lower alkyl, hydroxy, lower alkoxy, lower alkanoyl, lower alkanoyloxy, mercapto, lower alkylthio, $NR^{16}R^{17}$ (where R^{16} and R^{17} are same as R^9 and R^{10} , respectively), nitro, cyano, CO_2R^{18} (where R^{18} is same as R^{11}), $CONR^{19}R^{20}$ (where
 15 R^{19} and R^{20} are same as R^{12} and R^{13} , respectively), 4-oxo-2-thioxoimidazolidin-5-ylidenemethyl and halogen], substituted heteroaryl [where substituent(s) for the heteroaryl include one or more, up to the substitutable number of, substituents; preferably 1 to 5 substituents, such as lower alkyl, hydroxy, lower alkoxy, lower alkanoyl, lower alkanoyloxy, mercapto, lower alkylthio, $NR^{16a}R^{17a}$ (where R^{16a} and R^{17a} are same as R^9 and R^{10} ,
 20 respectively), nitro, cyano, CO_2R^{18a} (where R^{18a} is same as R^{11}), $CONR^{19a}R^{20a}$ (where R^{19a} and R^{20a} are same as R^{12} and R^{13} , respectively), 4-oxo-2-thioxoimidazolidin-5-ylidenemethyl and halogen], substituted aralkyl [where substituent(s) for the aralkyl include one or more, up to the substitutable number of, substituents; preferably 1 to 5 substituents, such as lower alkyl, hydroxy, lower alkoxy, lower alkanoyl, lower alkanoyloxy, mercapto, lower alkylthio,
 25 $NR^{16A}R^{17A}$ (where R^{16A} and R^{17A} are same as R^9 and R^{10} , respectively), nitro, cyano, CO_2R^{18A} (where R^{18A} is same as R^{11}), $CONR^{19A}R^{20A}$ (where R^{19A} and R^{20A} are same as R^{12} and R^{13} , respectively), 4-oxo-2-thioxoimidazolidin-5-ylidenemethyl and halogen], or substituted heteroarylalkyl [where substituent(s) for the heteroarylalkyl include one or more, up to the substitutable number of, substituents; preferably 1 to 5 substituents, such as lower alkyl,
 30 hydroxy, lower alkoxy, lower alkanoyl, lower alkanoyloxy, mercapto, lower alkylthio, $NR^{16Aa}R^{17Aa}$ (where R^{16Aa} and R^{17Aa} are same as R^9 and R^{10} , respectively), nitro, cyano, CO_2R^{18Aa} (where R^{18Aa} is same as R^{11}), $CONR^{19Aa}R^{20Aa}$ (where R^{19Aa} and R^{20Aa} are same as R^{12} and R^{13} , respectively), and halogen]; or alternatively, R^{14} and R^{15} together with the

nitrogen atom to which they are attached to form a substituted or unsubstituted heterocyclic group};

[67] nitro;

[68] cyano;

5 [69] CO_2R^{21} (where R^{21} is same as R^{11});

[70] $\text{CONR}^{22}\text{R}^{23}$ {where each of R^{22} and R^{23} is independently hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, substituted aryl [where substituent(s) for the aryl include one or more, up to the substitutable number of, substituents; preferably 1 to 5 substituents,

10 such as lower alkyl, trifluoromethyl, hydroxy, lower alkoxy, trifluoromethoxy, lower alkanoyl, lower alkanoyloxy, mercapto, lower alkylthio, aryl, $\text{NR}^{16\text{A}}\text{R}^{17\text{A}}$ (where $\text{R}^{16\text{A}}$ and $\text{R}^{17\text{A}}$ are same as R^9 and R^{10} , respectively), nitro, cyano, $\text{CO}_2\text{R}^{18\text{A}}$ (where $\text{R}^{18\text{A}}$ is same as R^{11}), $\text{CONR}^{19\text{A}}\text{R}^{20\text{A}}$ (where $\text{R}^{19\text{A}}$ and $\text{R}^{20\text{A}}$ are same as R^{12} and R^{13} , respectively),

arylsulfonylmethyl, methylenedioxy, propylenedioxy, and halogen], substituted aralkyl

15 [where substituent(s) for the aralkyl include one or more, up to the substitutable number of, substituents; preferably 1 to 5 substituents, such as lower alkyl, trifluoromethyl, hydroxy,

lower alkoxy, trifluoromethoxy, lower alkanoyl, lower alkanoyloxy, mercapto, lower alkylthio, aryl, $\text{NR}^{16\text{B}}\text{R}^{17\text{B}}$ (where $\text{R}^{16\text{B}}$ and $\text{R}^{17\text{B}}$ are same as R^9 and R^{10} , respectively), nitro, cyano, $\text{CO}_2\text{R}^{18\text{B}}$ (where $\text{R}^{18\text{B}}$ is same as R^{11}), $\text{CONR}^{19\text{B}}\text{R}^{20\text{B}}$ (where $\text{R}^{19\text{B}}$ and $\text{R}^{20\text{B}}$ are same as

20 R^{12} and R^{13} , respectively), arylsulfonylmethyl, methylenedioxy, propylenedioxy, and

halogen], substituted heteroaryl [where substituent(s) for the heteroaryl include one or more, up to the substitutable number of, substituents; preferably 1 to 5 substituents, such as lower

alkyl, trifluoromethyl, hydroxy, lower alkoxy, trifluoromethoxy, lower alkanoyl, lower

alkanoyloxy, mercapto, lower alkylthio, aryl, $\text{NR}^{16\text{Aa}}\text{R}^{17\text{Aa}}$ (where $\text{R}^{16\text{Aa}}$ and $\text{R}^{17\text{Aa}}$ are same as

25 R^9 and R^{10} , respectively), nitro, cyano, $\text{CO}_2\text{R}^{18\text{Aa}}$ (where $\text{R}^{18\text{Aa}}$ is same as R^{11}),

$\text{CONR}^{19\text{Aa}}\text{R}^{20\text{Aa}}$ (where $\text{R}^{19\text{Aa}}$ and $\text{R}^{20\text{Aa}}$ are same as R^{12} and R^{13} , respectively),

arylsulfonylmethyl, methylenedioxy, propylenedioxy, and halogen], substituted

heteroarylalkyl [where substituent(s) for the heteroarylalkyl include one or more, up to the substitutable number of, substituents; preferably 1 to 5 substituents, such as lower alkyl,

30 trifluoromethyl, hydroxy, lower alkoxy, trifluoromethoxy, lower alkanoyl, lower

alkanoyloxy, mercapto, lower alkylthio, aryl, $\text{NR}^{16\text{Ba}}\text{R}^{17\text{Ba}}$ (where $\text{R}^{16\text{Ba}}$ and $\text{R}^{17\text{Ba}}$ are same as R^9 and R^{10} , respectively), nitro, cyano, $\text{CO}_2\text{R}^{18\text{Ba}}$ (where $\text{R}^{18\text{Ba}}$ is same as R^{11}),

$\text{CONR}^{19\text{Ba}}\text{R}^{20\text{Ba}}$ (where $\text{R}^{19\text{Ba}}$ and $\text{R}^{20\text{Ba}}$ are same as R^{12} and R^{13} , respectively),

arylsulfonylmethyl, methylenedioxy, propylenedioxy, and halogen]; or alternatively, R^{22} and

R²³ together with the nitrogen atom to which they are attached to form a substituted or unsubstituted heterocyclic group}};

[71] arylsulfonylmethyl;

[72] methylenedioxy;

5 [73] propylenedioxy;

[74] halogen; and the like.

[75] In the aforementioned definitions of substituents for substituted aryl, substituted heteroaryl, substituted aralkyl, substituted heteroarylalkyl, substituted arylalkenyl, substituted heteroarylalkenyl, substituted arylalkynyl, substituted heteroarylalkynyl, substituted arylalkanoyl, substituted heteroarylalkanoyl, substituted arylalkenoyl, substituted heteroarylalkenoyl, substituted arylalkynoyl, and substituted heteroarylalkynoyl, lower alkyl, lower alkenyl, and lower alkynyl bear the same meanings as defined above, respectively.

Aryl bears the same definition as the aforementioned aryl in the definition of formula (I).

The aryl moiety of an aralkyl bears the same definition as the aforementioned aryl in the definition of formula (I). The alkylene moiety of an aralkyl represents the lower alkyl as defined above in the definition of formula (I) less one hydrogen atom. Heteroaryl bears the same definition as the aforementioned heteroaryl in the definition of formula (I). The heteroaryl moiety of a heteroarylalkyl bears the same definition as the aforementioned heteroaryl in the definition of formula (I). The alkylene moiety of a heteroarylalkyl represents the lower alkyl as defined above in the definition of formula (I) less one hydrogen atom. The aryl moiety of an arylsulfonylmethyl bears the same definition as the aforementioned aryl in the definition of formula (I). The aryl moiety of an arylalkenyl bears the same definition as the aforementioned aryl in the definition of formula (I). The alkenylene moiety of an arylalkenyl represents the lower alkenyl as defined above in the definition of formula (I) less one hydrogen atom. The heteroaryl moiety of a heteroarylalkenyl bears the same definition as the aforementioned heteroaryl in the definition of formula (I). The alkenylene moiety of a heteroarylalkenyl represents the lower alkenyl as defined above in the definition of formula (I) less one hydrogen atom. The aryl moiety of an arylalkynyl bears the same definition as the aforementioned aryl in the definition of formula (I). The alkynylene moiety of an arylalkynyl represents the lower alkynyl as defined above in the definition of formula (I) less one hydrogen atom. The heteroaryl moiety of a heteroarylalkynyl bears the same definition as the aforementioned heteroaryl in the definition of formula (I). The alkynylene moiety of a heteroarylalkynyl represents the lower alkynyl as defined above in the definition of formula (I) less one hydrogen atom. Halogen means an

iodine, bromine, chlorine, or fluorine atom. Examples of heterocyclic groups which may be formed together with the adjoining nitrogen atom include pyrrolidinyl, piperidino, piperazinyl, morpholino, thiomorpholino, pyrrolyl, imidazolyl, pyrazolyl, 1,2,3,6-tetrahydropyridyl, 1,2,3,4-tetrahydroisoquinolynyl, and the like. Substituents for a

heterocyclic group which may be formed together with the adjoining nitrogen atom are: lower alkyl, aralkyl, lower alkanoyl (where the lower alkyl moiety of the lower alkanoyl bears the same definition as above), aroyl, heteroaroyl, and substituted or unsubstituted aryl (where a substituent for the substituted aryl is lower alkyl, lower alkoxy, or halogen).

[76] Examples of substituents for substituted lower alkyl, substituted lower alkenyl, substituted lower alkynyl, substituted lower alkoxy, substituted lower alkanoyl, substituted lower alkenoyl, substituted lower alkynoyl, or substituted lower alkylthio include one or more, up to the substitutable number of, substituents; preferably 1 to 5 substituents; and more preferably 1 to 3 substituents, such as lower alkyl, lower alkenyl, lower alkynyl, hydroxy, lower alkoxy, lower alkoxy lower alkoxy, lower alkanoyl, lower alkanoyloxy, mercapto, lower alkylthio, cycloalkyl, cycloalkenyl, $\text{NR}^{24}\text{R}^{25}$ (where R^{24} and R^{25} are same as R^9 and R^{10}), nitro, cyano, CO_2R^{26} (where R^{26} is same as R^{11}), $\text{CONR}^{27}\text{R}^{28}$ (where R^{27} and R^{28} are same as R^{12} and R^{13}), aryl, heteroaryl, arylsulfonyl, alicyclic heterocyclic groups, halogen, and the like.

[77] In the aforementioned definitions of substituents for substituted lower alkyl, substituted lower alkenyl, substituted lower alkynyl, substituted lower alkoxy, substituted lower alkanoyl, substituted lower alkenoyl, substituted lower alkynoyl, or substituted lower alkylthio, lower alkyl bears the same definition as above; and the lower alkyl moiety of lower alkoxy, lower alkanoyl, lower alkanoyloxy, or lower alkylthio bears the same definition as the aforementioned lower alkyl. Lower alkenyl and lower alkynyl bear the same definitions as lower alkenyl and lower alkyl as defined above, respectively. Cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like, having 3 to 8 carbons. Cycloalkenyl includes cyclopentenyl, cyclohexenyl, and the like, having 5 to 8 carbons. Lower alkoxy lower alkoxy means a lower alkoxy which has been substituted with lower alkoxy. Examples of alicyclic heterocyclic groups include tetrahydrofuranyl, tetrahydropyranlyl, 2-pyrrolidon-1-yl, and the like. Aryl bears the same definition as the aforementioned aryl in the definition of formula (I). Heteroaryl bears the same definition as the aforementioned heteroaryl in the definition of formula (I). The aryl moiety of the arylsulfonyl bears the same definition as the aforementioned aryl in the definition of formula (I). Halogen bears the same definition as above.

[78] Respective groups in formula (Ia) are subject to the following definitions. Examples of lower alkyl include those which have 1 to 6 carbons and which are in a straight chain or branched form, e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, and hexyl.

5 [79] Examples of lower alkenyl include those which have 2 to 10 carbons and which are in a straight chain or branched form, e.g., vinyl, propenyl, methacryl, prenyl, butenyl, pentenyl, hexenyl, and geranyl.

[80] Examples of lower alkynyl include those which have 2 to 6 carbons and which are in a straight chain or branched form, e.g., ethynyl, propynyl, butynyl, pentynyl, and
10 hexynyl.

[81] The alkylene moieties of aralkyl or heteroarylalkyl represents the aforementioned lower alkyl less one hydrogen atom. The alkenylene moiety of arylalkenyl or heteroarylalkenyl represents the aforementioned lower alkenyl less one hydrogen atom. The alkynylene moiety of arylalkynyl or heteroarylalkynyl represents the aforementioned lower
15 alkynyl less one hydrogen atom. The lower alkyl moiety of lower alkoxy, lower alkylthio, or lower alkanoyl bears the same definition as the aforementioned lower alkyl.

[82] "Halogen" means iodine, bromine, chlorine, or fluorine.

[83] Examples of aryl include phenyl, naphthyl, and the like.

[84] Examples of heteroaryl include pyridyl, thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, pyrimidinyl, oxazolyl, thiazolyl, indolyl, and the like. The aryl moiety of aralkyl, arylalkenyl, arylalkynyl, aryloxy, and aralkyloxy bears the same definition as the
20 aforementioned aryl in the definition of formula (Ia). The heteroaryl moiety of heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroaryloxy, and heteroarylalkyloxy bears the same definition as the heteroaryl in the definition of formula (Ia).

25 [85] Exemplary heterocyclic groups which may be formed together with the adjoining nitrogen atom include pyrrolidinyl, piperidino, piperazinyl, morpholino, thiomorpholino, pyrrolyl, imidazolyl, pyrazolyl, 1,2,3,6-tetrahydropyridyl, 1,2,3,4-tetrahydroisoquinolynyl, and the like. Substituents for a substituted heterocyclic group which may be formed together with the adjoining nitrogen atom include: lower alkyl, aralkyl, lower
30 alkanoyl, aroyl, heteroaroyl, and substituted or unsubstituted aryl (where a substituent for substituted aryl is lower alkyl, lower alkoxy, or halogen).

[86] In the definition of substituents for the substituted heterocyclic group which may be formed together with the adjoining nitrogen atom, lower alkyl and aralkyl bear the same definitions as the lower alkyl and aralkyl in the definition of formula (Ia), respectively.

The lower alkyl moiety of the lower alkanoyl bears the same definition as the lower alkyl in the definition of formula (Ia). The aryl moiety of aroyl bears the same definition as aryl in the definition of formula (Ia). The heteroaryl moiety of heteroaroyl bears the same definition as heteroaryl in the definition of formula (Ia). Aryl bears the same definition as aryl in the definition of formula (Ia). Lower alkoxy and halogen bear the same definition as the lower alkyl and halogen in the definition of formula (Ia).

[87] Examples of substituents for substituted aryl, substituted naphthyl, substituted heteroaryl, substituted aralkyl, substituted heteroarylalkyl, substituted arylalkenyl, substituted heteroarylalkenyl, substituted arylalkynyl, or substituted heteroarylalkynyl, may be the same or different, and include one or more, up to the substitutable number of, substituents; preferably 1 to 3 substituents, such as lower alkyl, trifluoromethyl, hydroxy, lower alkoxy, trifluoromethoxy, mercapto, lower alkylthio, aryl, $\text{NR}^{29}\text{R}^{30}$ (where R^{29} and R^{30} may be the same or different and respectively bear the same definitions as the aforementioned R^9 and R^{10}), nitro, cyano, CO_2R^{31} (where R^{31} bears the same definitions as the aforementioned R^{11}), $\text{CONR}^{32}\text{R}^{33}$ (where R^{32} and R^{33} may be the same or different and respectively bear the same definitions as the aforementioned R^{12} and R^{13}), arylsulfonylmethyl, methylenedioxy, propylenedioxy, or halogen.

[88] In the aforementioned definitions of substituents for substituted aryl, substituted naphthyl, substituted heteroaryl, substituted aralkyl, substituted heteroarylalkyl, substituted arylalkenyl, substituted heteroarylalkenyl, substituted arylalkynyl, and substituted heteroarylalkynyl, lower alkyl bears the same definition as the lower alkyl in the definition of formula (Ia). The lower alkyl moiety of lower alkoxy or lower alkylthio bears the same definition as the lower alkyl in the definition of formula (Ia). Aryl bears the same definition as the aryl in the definition of formula (Ia). The aryl moiety of arylsulfonylmethyl bears the same definition as the aryl in the definition of formula (Ia). Halogen bears the same definition as the halogen in the definition of formula (Ia).

[89] Examples of substituents for substituted lower alkyl, substituted lower alkenyl, substituted lower alkynyl, substituted lower alkoxy, or substituted lower alkylthio may be the same or different, and include one or more, up to the substitutable number of, substituents; preferably 1 to 3 substituents, such as lower alkyl, lower alkenyl, lower alkynyl, hydroxy, lower alkoxy, lower alkoxy lower alkoxy, mercapto, lower alkylthio, cycloalkyl, cycloalkenyl, $\text{NR}^{34}\text{R}^{35}$ (where R^{34} and R^{35} are same as R^9 and R^{10} , respectively), nitro, cyano, CO_2R^{36} (where R^{36} is same as R^{11}), aryl, heteroaryl, arylsulfonyl, alicyclic heterocyclic group and halogen.

[90] In the aforementioned definitions of the substituents for substituted lower alkyl, substituted lower alkenyl, substituted lower alkynyl, substituted lower alkoxy, or substituted lower alkylthio, lower alkyl, lower alkenyl, and lower alkynyl bear the same definitions as the lower alkyl, lower alkenyl, and lower alkynyl in the definition of formula (Ia), respectively. The lower alkyl moiety of lower alkoxy and lower alkylthio bears the same definition as the lower alkyl in the definition of formula (Ia). Cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like, having 3 to 8 carbons. Cycloalkenyl includes cyclopentenyl, cyclohexenyl, and the like, having 5 to 8 carbons. Lower alkoxy lower alkoxy means a lower alkoxy group which is substituted with lower alkoxy. Aryl bears the same definition as aryl in the definition of formula (Ia). Heteroaryl bears the same definition as heteroaryl in the definition of formula (Ia). The aryl moiety of arylsulfonyl bears the same definition as aryl in the definition of formula (Ia). Examples of alicyclic heterocyclic groups include tetrahydrofuranyl, tetrahydropyranyl, 2-pyrrolidon-1-yl, and the like. Halogen bears the same definition as halogen in the definition of formula (Ia).

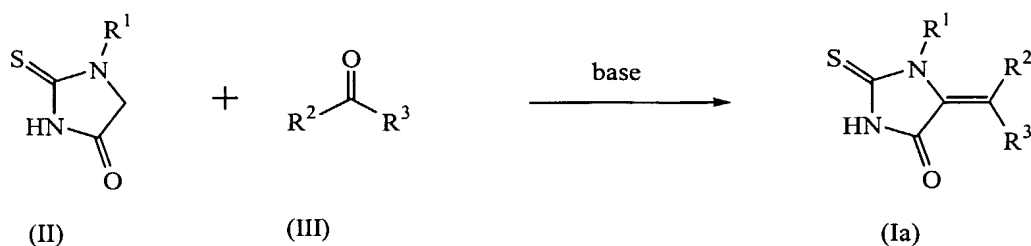
[91] Exemplary pharmaceutically acceptable salts of Compound (I) include pharmaceutically acceptable acid addition salts or base addition salts, such as: inorganic acid salts, e.g., hydrochlorides, hydrobromides, sulfates, and phosphates; organic acid salts, e.g., methanesulfonates, oxalates, acetates, malonates, succinates, fumarates, maleates, tartrates, and citrates; and base addition salts, e.g., sodium salts, potassium salts, and calcium salts.

[92] Some species of Compound (I) according to the present invention may have various stereoisomers, regioisomers, tautomers, and the like. It is intended that all such possible isomers and mixtures thereof can be used for the telomerase inhibitor or antitumor agent according to the present invention, the mixture ratio being arbitrarily selected.

[93] Compound (I) may in itself be commercially available. Any species thereof which are not commercially available or are novel can be synthesized in a method similar to the following method for producing Compound (Ia) or methods individually described in Examples, etc.

[94] If any of the defined groups are susceptible to unwanted modification under the described conditions or otherwise unsuitable for practicing the production method described below, it is possible to adopt a method commonly used in synthetic organic chemistry, e.g., protection and deprotection of functional groups to facilitate production [see Protective Groups in Organic Synthesis, T.W. Greene, John Wiley & Sons, Inc. (1981), etc.]. The order of reaction steps, such as introduction of substituents, may be altered if necessary.

[95] Compound (Ia) can be produced through the following reaction step.



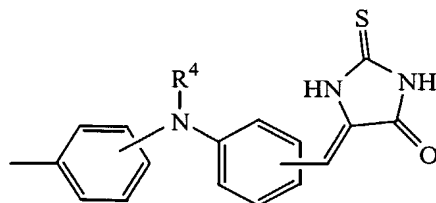
where R¹, R², and R³ are those defined above.

[96] Compound (Ia) can be obtained by reacting a 4-oxo-2-thioxoimidazolidine derivative (II), as commercially available or obtained by the method described later, with a carbonyl Compound (III), as commercially available or obtained by the method described later.

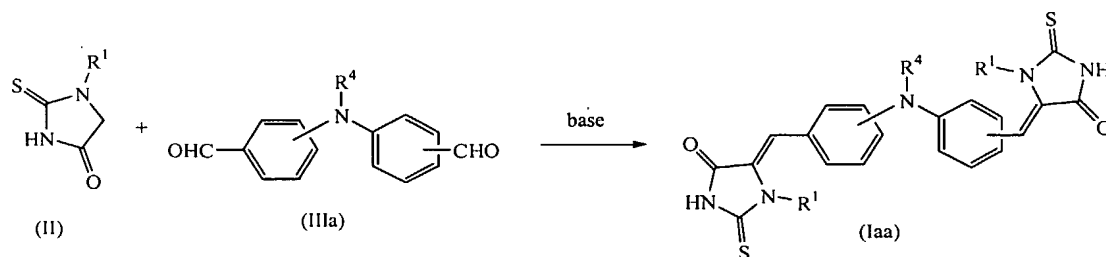
[97] The reaction can be carried out in the presence of a base catalyst, in a solvent if necessary. Examples of the base catalyst include piperidine, piperidinium acetate, diethylamine, pyridine, sodium acetate, potassium carbonate, sodium carbonate, lithium hydroxide, sodium hydroxide, potassium hydroxide, and the like. Such base catalysts may be used in 0.1 to 1 equivalent of Compound (III). Suitable solvents include alcohols, such as methanol, ethanol, propanol; ethers, such as diethyl ether, tetrahydrofuran, dioxane; hydrocarbons, such as benzene, toluene, xylene; N,N-dimethylformamide; N-methylpyrrolidinone and a combination thereof.

[98] Compound (II) and Compound (III) may be used in equivalent molar amounts, although in some cases Compound (III) may be used in 0.5 to 2 equivalents of Compound (II). The reaction is carried out at a temperature range from room temperature to the boiling point of the solvent, preferably from room temperature to 100 °C. The reaction time is typically from 1 to 50 hours.

[99] Compound (Iaa), i.e., Compound (Ia) in which one of R² or R³ is hydrogen, and the other is



(where R¹ and R⁴ are those defined above), can be produced through the following reaction step.

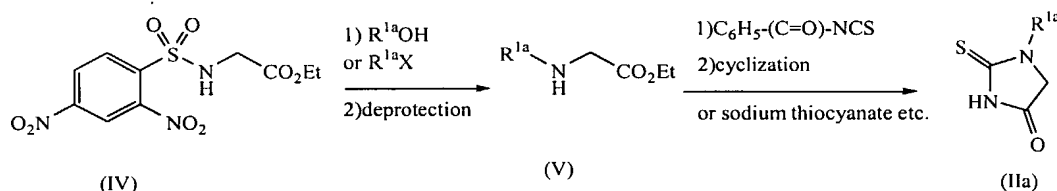


where R^1 and R^4 are those defined above.

[100] Compound (Iaa) can be obtained by reacting Compound (IIIa) with 2 to 4 equivalents of Compound (II) in a manner similar to obtaining Compound (Ia) from Compound (II) and Compound (III).

[101] Next, a method for producing Compound (II) to serve as a starting material will be described.

[102] Compound (IIa), i.e., Compound (II) in which R^1 is not hydrogen, can be obtained through the following reaction steps.



where R^{1a} represents a group according to the definition of aforementioned R^1 other than hydrogen; and X represents chlorine, bromine, iodine, p-toluenesulfonyloxy or methanesulfonyloxy.

[103] Compound (V) can be produced in a method similar to that disclosed in *Tetrahedron Letters*, vol. 38, pp. 5831-5834 (1997). Briefly, in an ether solvent such as diethyl ether, tetrahydrofuran, or dioxane, or in an aromatic hydrocarbon solvent such as benzene, toluene, or xylene, Compound (IV) is allowed to react with $R^{1a}OH$ (where R^{1a} is that defined above) for 1 to 24 hours at a temperature range of from room temperature to the boiling point of the solvent in the presence of triphenylphosphine or the like, and diethyl azodicarboxylate, diisopropyl azodicarboxylate, or the like. Or alternatively, in an alcohol solvent such as ethanol, methanol or propanol in an ether solvent such as diethyl ether, tetrahydrofuran or dioxane, or in a solvent such as N,N-dimethylformamide or N-methylpyrrolidinone, Compound (IV) is allowed to react with $R^{1a}X$ (where R^{1a} and X are those defined above) for 1 to 24 hours at a temperature range of from room temperature to the boiling point of the solvent in the presence of a base, such as potassium carbonate, sodium carbonate, sodium hydride, sodium ethoxide or potassium tert-butoxide. Thereafter, in an

ether solvent such as diethyl ether, tetrahydrofuran, or dioxane, or in a halomethane solvent, such as methylene chloride or chloroform, treatment of the product with a thiol, such as mercaptoacetic acid or ethyl mercaptoacetate is performed for 1 to 24 hours at a temperature in the range from room temperature to the boiling point of the solvent, if necessary in the presence of an organic base such as triethylamine. As a result, the 2,4-dinitrobenzenesulfonyl group is deprotected, whereby Compound (V) can be produced.

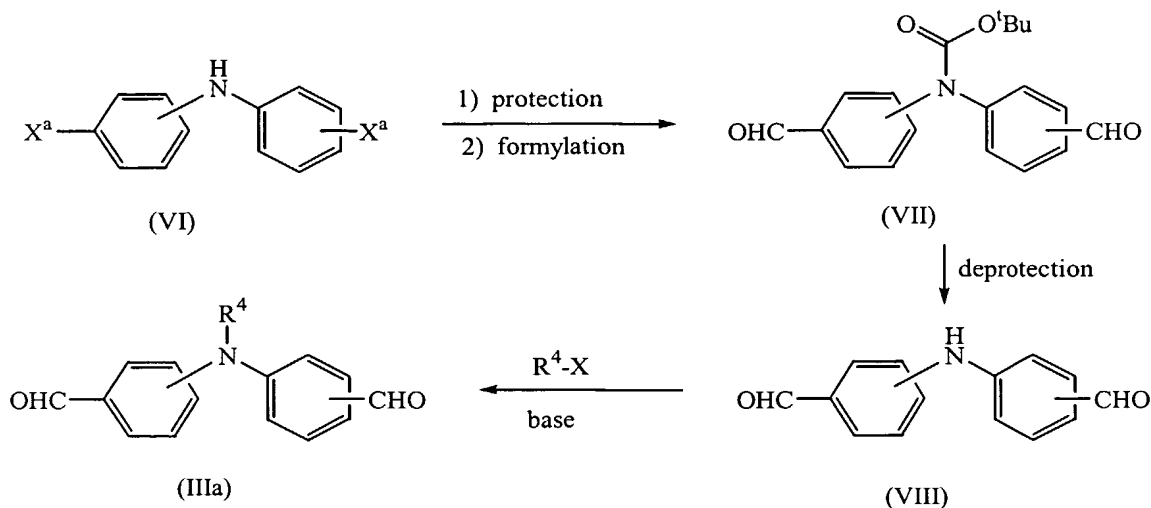
[104] Next, the Compound (V) and benzoyl isothiocyanate are allowed to react for 1 to 24 hours at a temperature range of from room temperature to the boiling point of the solvent, e.g., halomethane solvent, such as methylene chloride or chloroform; or ether solvent, such as diethyl ether, tetrahydrofuran or dioxane. Then, in the presence of an organic base such as propylamine or benzylamine, and preferably in the presence of aminomethylated polystyrene, a treatment is performed as to the product for 1 to 24 hours at a temperature in the range from room temperature to the boiling point of the solvent in a halomethane solvent such as methylene chloride or chloroform, or in an ether solvent such as ether, tetrahydrofuran, or dioxane, thereby effecting cyclization reaction and deprotection of the benzoyl group after cyclization. Alternatively, Compound (V) and sodium thiocyanate, potassium thiocyanate or the like are allowed to react for 1 to 24 hours at a temperature in the range from room temperature to the boiling point of the solvent in an alcohol solvent such as methanol, ethanol, or propanol, or in a mixed solvent containing the same and water, if necessary with pH adjustment using acetic acid or the like. Thus, Compound (IIa) can be produced.

[105] Next, a method for producing Compound (III) to serve as a starting material will be described.

[106] Compound (IIIa), i.e., Compound (III) in which one of R^2 or R^3 is hydrogen and the other is



(where R^4 is that defined above), can be produced through the following reaction steps.



where R^4 and X are those defined above; and X^a represents a group according to the definition of aforementioned X other than chlorine.

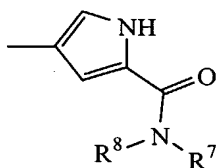
[107] In a halomethane solvent such as methylene chloride or chloroform, or in an ether solvent such as ether, tetrahydrofuran, or dioxane, if necessary in the presence of an organic base such as triethylamine, pyridine, or 4-dimethylaminopyridine, Compound (VI) and di-tert-butyl dicarbonate are allowed to react for 1 to 24 hours at a temperature in the range from room temperature to the boiling point of the solvent, whereby a compound, in which the amino group in Compound (VI) is protected can be obtained. After an organic lithium reagent, such as n-butyl lithium or methyl lithium, is allowed to react with the obtained compound at a temperature range of from -78°C to 0°C for 10 minutes to 12 hours in an ether solvent such as diethyl ether, tetrahydrofuran, or dioxane, a formylating reagent such as N,N-dimethylformamide is allowed to react with the product for 30 minutes to 24 hours at a temperature in the range from -78°C to room temperature, whereby Compound (VII) can be produced.

[108] Compound (VIII) can be produced by adding an organic acid such as trifluoroacetic acid or a mineral acid such as hydrogen chloride or hydrogen bromide to Compound (VII) in a halomethane solvent such as methylene chloride or chloroform, or in an ether solvent such as ether, tetrahydrofuran, or dioxane, and carrying out a treatment of the mixture at a temperature range of from 0°C to the boiling point of the solvent for 1 to 24 hours.

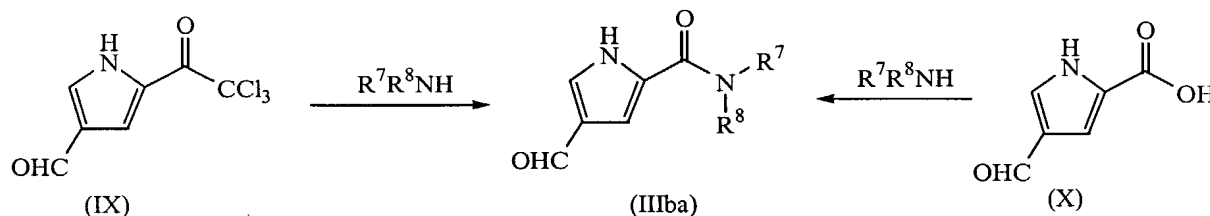
[109] Compound (IIIa) can be produced by allowing Compound (VIII) to react with R^4X (where R^4 and X are those defined above) at a temperature range of from room temperature to the boiling point of the solvent for 1 to 24 hours in an ether solvent such as

ether, tetrahydrofuran, or dioxane, or in a solvent such as N,N-dimethylformamide or N-methylpyrrolidinone, in the presence of a base such as sodium hydride, potassium hydride, or potassium tert-butoxide.

[110] Compound (IIIba), i.e., Compound (III) in which one of R^2 or R^3 is hydrogen and the other is



(where R^7 and R^8 are those defined above), can be produced through the following reaction steps.



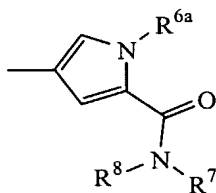
where R^7 and R^8 are those defined above.

[111] Compound (IIIba) can be produced by allowing Compound (IX) (*J. Org. Chem.*, vol. 43, pp. 4849-4853 (1978)) to react with 1 to 4 equivalents, and preferably 1 to 2 equivalents of amine R^7R^8NH , at a temperature range of from -78°C to the boiling point of the solvent, preferably at a temperature range of from room temperature to the boiling point of the solvent, for 1 to 72 hours, preferably 1 to 48 hours, in a solvent such as N,N-dimethylformamide or tetrahydrofuran in the absence of a base, or in the presence of a base such as 1 to 4 equivalents, preferably 1 to 2 equivalents of potassium carbonate, sodium carbonate, cesium carbonate, sodium hydride, potassium tert-butoxide or the like, or 1 to 4 equivalents, preferably 1 to 1.5 equivalents of n-butyl lithium or the like.

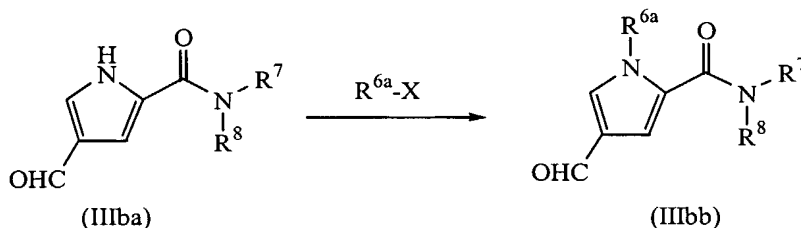
[112] Alternatively, Compound (IIIba) can also be produced by reacting Compound (X) (*Synth. Commun.*, vol. 17, pp. 401-407 (1987)) with 1 to 4 equivalents, preferably 1 to 2 equivalents, of amine R^7R^8NH at a temperature range of from 0°C to the boiling point of the solvent, preferably at a temperature range of from room temperature to the boiling point of the solvent, for 1 to 72 hours, preferably 1 to 48 hours, in a halomethane solvent such as methylene chloride or chloroform, or in a solvent such as N,N-dimethylformamide or tetrahydrofuran, in the presence of 1 to 4 equivalents, and preferably 1 to 2 equivalents of a condensing agent such as dicyclohexylcarbodiimide or 1-(3-

dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. Alternatively, Compound (IIIba) can also be produced by allowing an acid halide - which can be produced by halogenating Compound (X) in an inert solvent such as methylene chloride by employing 1 equivalent to the solvent amount, preferably 1 to 2 equivalents, of a halogenating agent such as thionyl chloride, at a temperature range of from 0 °C to the boiling point of the solvent, preferably at a temperature range of from room temperature to the boiling point of the solvent, for 1 to 72 hours, preferably 1 to 5 hours - to react with 1 to 4 equivalents, preferably 1 to 2 equivalents, of a primary or secondary amine at a temperature range of from 0 °C to the boiling point of the solvent, preferably at a temperature range of from room temperature to the boiling point of the solvent, for 1 to 72 hours, preferably 1 to 24 hours, in a solvent such as methylene chloride, chloroform, N,N-dimethylformamide, tetrahydrofuran, 1,2-dimethoxyethane, or 1,4-dioxane, in the presence of 1 equivalent to the solvent amount, preferably 1 to 5 equivalents of an organic base such as pyridine or triethylamine.

[113] Compound (IIIbb), i.e., Compound (III) in which one of R² or R³ is hydrogen and the other is



(where R^{6a} represents a group according to the definition of R⁶ other than hydrogen; and R⁷ and R⁸ are those defined above), can be produced through the following reaction step:

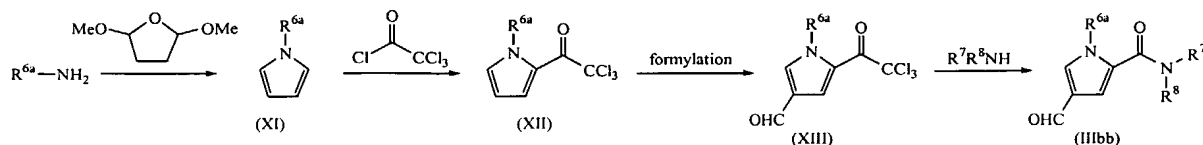


where, R^{6a}, R⁷, R⁸ and X are those defined above.

[114] Compound (IIIbb) can be produced by allowing Compound (IIIba) and 1 to 4 equivalents, preferably 1 to 2 equivalents of a compound represented as R^{6a}-X (where R^{6a} and X are those defined above) to react at a temperature range of from 0 °C to the boiling point of the solvent, preferably at a temperature range of from room temperature to the boiling point of the solvent, for 1 to 72 hours, preferably 1 to 48 hours, in a inert solvent such as N,N-dimethylformamide, tetrahydrofuran, dimethoxyethane, or 1,4-dioxane, in the presence of an organic base such as 1 to 4 equivalents, preferably 1 to 2 equivalents of sodium carbonate,

cesium carbonate, sodium hydride or potassium tert-butoxide, or 1 to 4 equivalents, preferably 1 to 1.5 equivalents of 2-(tert-butylimino)-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphospholine, 2-(tert-butylimino)-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphospholine on polystyrene, or 1,8-diazabicyclo[4.3.0]undec-7-ene.

- 5 [115] Alternatively, Compound (IIIbb) can also be produced through the following reaction steps.



where R^{6a} , R^7 and R^8 are those defined above.

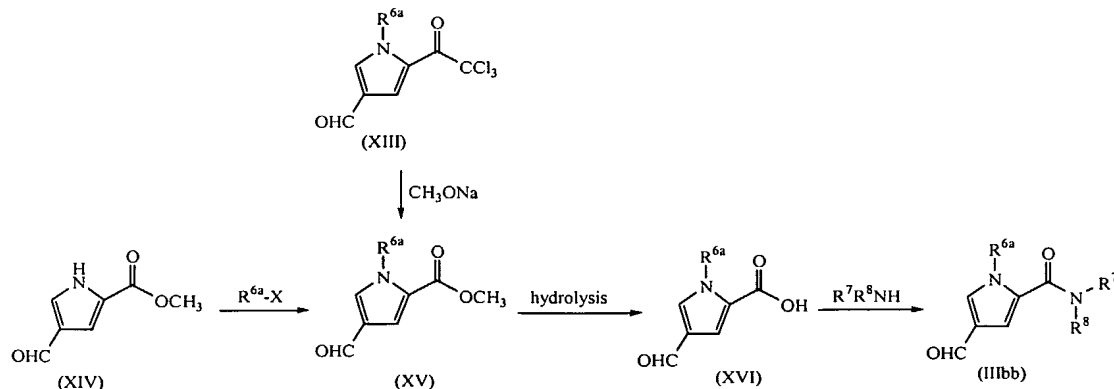
- [116] Compound (XI) can be produced from a compound represented by $R^{6a}NH_2$ (where R^{6a} is that defined above) and 2,5-dimethoxytetrahydrofuran, according to a method similar to that described in literature [*J. Org. Chem.*, vol. 63, pp. 6715-6718 (1998)].

[117] Compound (XII) can be produced from Compound (XI) and trichloroacetyl chloride in a method similar to that described in literature [*J. Org. Chem.*, vol. 43, pp. 4849-4853 (1978)].

- 15 [118] Compound (XIII) can be produced by subjecting Compound (XII) to formylation in a method similar to that described in literature [*J. Org. Chem.*, vol. 43, pp. 4849-4853 (1978)].

[119] Compound (IIIbb) can be produced from Compound (XIII) and a compound represented by R^7R^8NH in a method similar to that for obtaining Compound (IIIba) from Compound (IX).

- [120] Alternatively, Compound (IIIbb) can also be produced through the following reaction steps.



where R^{6a} , R^7 and R^8 are those defined above.

[121] Compound (XV) can be produced from Compound (XIV) in a method similar to that for obtaining Compound (IIIbb) from Compound (IIIba). Alternatively, Compound (XV) can be produced by allowing Compound (XIII) and 1 to 4 equivalents, preferably 1 to 2 equivalents of sodium methoxide to react in methanol at a temperature range of from 0 °C to the boiling point of the solvent, preferably at a temperature range of from room temperature to the boiling point of the solvent, for 1 to 72 hours, preferably 1 to 48 hours.

[122] Compound (XVI) can be produced by hydrolyzing Compound (XV) in a solvent such as methanol or ethanol, in the presence of 1 to 4 equivalents, preferably 1 to 2 equivalents of an aqueous solution of sodium hydroxide, an aqueous solution of potassium hydroxide, an aqueous solution of lithium hydroxide or the like, at a temperature range of from 0 °C to the boiling point of the solvent, preferably at a temperature range of from room temperature to the boiling point of the solvent, for 1 to 72 hours, preferably 1 to 48 hours.

[123] Compound (IIIbb) can be produced from Compound (XVI) in a method similar to that for producing Compound (IIIba) from Compound (X).

[124] A desired compound according to each of the above-described production method may be isolated and purified by a purification method which is commonly used in synthetic organic chemistry, e.g., filtration, extraction, washing, drying, concentration, recrystallization, and/or various chromatography techniques. Furthermore, the desired compound may be purified by a purification method which is commonly used in general parallel synthesis methods, e.g., methods using scavenger resin and/or ion exchange resin techniques.

[125] A salt of Compound (I) can be obtained from a free form of Compound (I) by forming a salt by usual methods. For example, Compound (I) can be dissolved or suspended in an appropriate solvent and a predetermined acid or base can be added. The resulting salt can then be isolated and/or purified. Alternatively, a salt of Compound (I) can be obtained directly from the reaction and optionally be purified.

[126] Compound (I) or a pharmaceutically acceptable salt thereof may be in the form of an adduct with water or various solvents. Such adducts are also encompassed within the present invention.

[127] Compound (I) or a pharmaceutically acceptable salt thereof may be used as such or in various forms of pharmaceutical formulations depending on the pharmacological effects and purpose of administration thereof. When used as a drug, an effective amount of Compound (I) or a pharmaceutically acceptable salt thereof may be uniformly mixed with a

pharmaceutically acceptable carrier. Such a carrier may be in a wide range of forms depending on the particular formulation desired for administration. Such a drug composition is preferably in a unit dosage form appropriate for oral or parenteral administration (e.g., via injection).

5 **[128]** Tablets can be formulated using any of the conventional methods known to one skill in the art and can include an excipient, a disintegrator, a lubricant, a binder and/or a surfactant. Exemplary excipients include lactose, glucose, sucrose, mannitol, methyl cellulose, and the like. Exemplary disintegrators include starch, sodium alginate, carboxymethyl cellulose calcium, crystalline cellulose, and the like. Exemplary lubricants
10 include magnesium stearate, talc, and the like. Exemplary binders include gelatin, polyvinylalcohol, polyvinylpyrrolidone, hydroxypropyl cellulose, methyl cellulose, and the like. Exemplary surfactants include sucrose fatty acid esters, sorbitan fatty acid esters, and the like. Such tablets preferably contain 1 to 300 mg of an active ingredient per tablet.

[129] Granules can be prepared using any of the conventional methods known to one
15 skilled in the art by adding suitable components, e.g., excipients such as lactose or sucrose; disintegrators such as starch; and/or binders such as gelatin. Similarly, powder forms can be prepared using any of the conventional methods known to one skilled in the art by adding suitable components, for example, an excipient, such as lactose or mannitol.

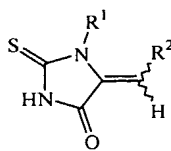
[130] Capsule formulation can include gelatin, water, sucrose, gum Arabic, sorbitol,
20 glycerin, crystalline cellulose, magnesium stearate talc, and/or the like. Such capsules preferably contain 1 to 300 mg of an active ingredient per capsule.

[131] Injectable form can include a solvent, such as water, saline, vegetable oils (e.g., olive oil or peanut oil), ethyl oleate or propylene glycol; a solubilizer, such as sodium benzoate, sodium salicylate, and urethane; an isotonicizing agent, such as sodium chloride or
25 glucose; a preservative, such as phenol, cresol, p-hydroxy benzoate, or chlorobutanol; an antioxidant, such as ascorbic acid or sodium pyrosulfite; and the like.

[132] Compound (I) or a pharmaceutically acceptable salt thereof can be orally or parenterally (e.g., via injection) administered. Although the effective dose and administration frequency may vary depending on the mode of administration, the age, weight, and/or
30 symptoms of each patient and/or the like, it is generally preferable to administer 0.01 to 20 mg/kg of Compound (I) or a pharmaceutically acceptable salt thereof, over one to four times per day.

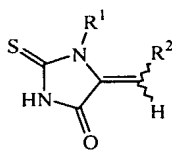
[133] Specific examples Compound (I) are shown in Tables 1 to 3 below. However, it should be appreciated that the scope of the present invention is not limited to such specific examples.

Table 1-1



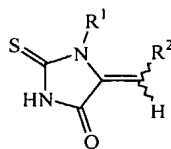
Cpd. No.	R ¹	R ²	Instrumental Data
1	—(CH ₂) ₂ CH ₃		MS m/z (M-H) ⁻ 245
2	—(CH ₂) ₂ CH ₃		MS m/z (M-H) ⁻ 251
3	—(CH ₂) ₂ CH ₃		MS m/z (M-H) ⁻ 270
4	—(CH ₂) ₂ CH ₃		MS m/z (M-H) ⁻ 246
5	—(CH ₂) ₂ CH ₃		MS m/z (M-H) ⁻ 275
6	—(CH ₂) ₂ CH ₃		MS m/z (M-H) ⁻ 301
7	—(CH ₂) ₂ CH ₃		MS m/z (M-H) ⁻ 263
8	—(CH ₂) ₂ CH ₃		MS m/z (M-H) ⁻ 305
9	—(CH ₂) ₂ CH ₃		MS m/z (M-H) ⁻ 287
10	—(CH ₂) ₂ CH ₃		MS m/z (M-H) ⁻ 290
11	—(CH ₂) ₂ CH ₃		MS m/z (M-H) ⁻ 337
12	—(CH ₂) ₂ CH ₃		MS m/z (M-H) ⁻ 382

Table 1-2



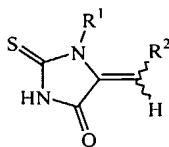
Cpd. No.	R ¹	R ²	Instrumental Data
13	—(CH ₂) ₂ OCH ₃		MS m/z (M-H) ⁻ 261
14	—(CH ₂) ₂ OCH ₃		MS m/z (M-H) ⁻ 267
15	—(CH ₂) ₂ OCH ₃		MS m/z (M-H) ⁻ 286
16	—(CH ₂) ₂ OCH ₃		MS m/z (M-H) ⁻ 262
17	—(CH ₂) ₂ OCH ₃		MS m/z (M-H) ⁻ 291
18	—(CH ₂) ₂ OCH ₃		MS m/z (M-H) ⁻ 317
19	—(CH ₂) ₂ OCH ₃		MS m/z (M-H) ⁻ 279
20	—(CH ₂) ₂ OCH ₃		MS m/z (M-H) ⁻ 321
21	—(CH ₂) ₂ OCH ₃		MS m/z (M-H) ⁻ 303
22	—(CH ₂) ₂ OCH ₃		MS m/z (M-H) ⁻ 305
23	—(CH ₂) ₂ OCH ₃		MS m/z (M-H) ⁻ 353
24	—(CH ₂) ₂ OCH ₃		MS m/z (M-H) ⁻ 397

Table 1-3



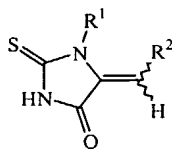
Cpd. No.	R ¹	R ²	Instrumental Data
25			MS m/z (M-H) ⁻ 273
26			MS m/z (M-H) ⁻ 279
27			MS m/z (M-H) ⁻ 298
28			MS m/z (M-H) ⁻ 274
29			MS m/z (M-H) ⁻ 303
30			MS m/z (M-H) ⁻ 329
31			MS m/z (M-H) ⁻ 291
32			MS m/z (M-H) ⁻ 333
33			MS m/z (M-H) ⁻ 315
34			MS m/z (M-H) ⁻ 317
35			MS m/z (M-H) ⁻ 365
36			MS m/z (M-H) ⁻ 409

Table 1-4



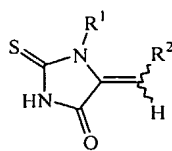
Cpd. No.	R ¹	R ²	Instrumental Data
37			MS m/z (M-H) ⁻ 313
38			MS m/z (M-H) ⁻ 319
39			MS m/z (M-H) ⁻ 338
40			MS m/z (M-H) ⁻ 314
41			MS m/z (M-H) ⁻ 343
42			MS m/z (M-H) ⁻ 369
43			MS m/z (M-H) ⁻ 331
44			MS m/z (M-H) ⁻ 373
45			MS m/z (M-H) ⁻ 355
46			MS m/z (M-H) ⁻ 357
47			MS m/z (M-H) ⁻ 405
48			MS m/z (M-H) ⁻ 449

Table 1-5



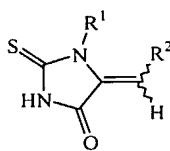
Cpd. No.	R ¹	R ²	Instrumental Data
49			MS m/z (M-H) ⁻ 293
50			MS m/z (M-H) ⁻ 299
51			MS m/z (M-H) ⁻ 318
52			MS m/z (M-H) ⁻ 294
53			MS m/z (M-H) ⁻ 323
54			MS m/z (M-H) ⁻ 349
55			MS m/z (M-H) ⁻ 311
56			MS m/z (M-H) ⁻ 353
57			MS m/z (M-H) ⁻ 335
58			MS m/z (M-H) ⁻ 337
59			MS m/z (M-H) ⁻ 385 ¹ H NMR: See Example
60			MS m/z (M-H) ⁻ 429

Table 1-6



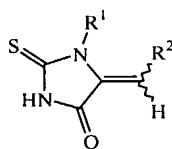
Cpd. No.	R ¹	R ²	Instrumental Data
61			MS m/z (M-H) ⁻ 299
62			MS m/z (M-H) ⁻ 305
63			MS m/z (M-H) ⁻ 324
64			MS m/z (M-H) ⁻ 300
65			MS m/z (M-H) ⁻ 329
66			MS m/z (M-H) ⁻ 355
67			MS m/z (M-H) ⁻ 317
68			MS m/z (M-H) ⁻ 359
69			MS m/z (M-H) ⁻ 341
70			MS m/z (M-H) ⁻ 343
71			MS m/z (M-H) ⁻ 391
72			MS m/z (M-H) ⁻ 435

Table 1-7



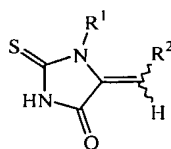
Cpd. No.	R ¹	R ²	Instrumental Data
73			MS m/z (M-H) ⁺ 301
74			MS m/z (M-H) ⁺ 307
75			MS m/z (M-H) ⁺ 326
76			MS m/z (M-H) ⁺ 302
77			MS m/z (M-H) ⁺ 331
78			MS m/z (M-H) ⁺ 357
79			MS m/z (M-H) ⁺ 319
80			MS m/z (M-H) ⁺ 361
81			MS m/z (M-H) ⁺ 343
82			MS m/z (M-H) ⁺ 345
83			MS m/z (M-H) ⁺ 393
84			MS m/z (M-H) ⁺ 437

Table 1-8



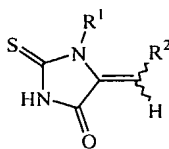
Cpd. No.	R ¹	R ²	Instrumental Data
85			MS m/z (M-H) ⁻ 327
86			MS m/z (M-H) ⁻ 333
87			MS m/z (M-H) ⁻ 352
88			MS m/z (M-H) ⁻ 328
89			MS m/z (M-H) ⁻ 357
90			MS m/z (M-H) ⁻ 383
91			MS m/z (M-H) ⁻ 345
92			MS m/z (M-H) ⁻ 387
93			MS m/z (M-H) ⁻ 369
94			MS m/z (M-H) ⁻ 371
95			MS m/z (M-H) ⁻ 419
96			MS m/z (M-H) ⁻ 463

Table 1-9



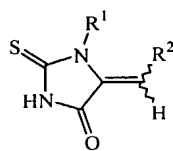
Cpd. No.	R ¹	R ²	Instrumental Data
97	—(CH ₂) ₂ CH ₃		MS m/z (M-H) ⁻ 289
98	—(CH ₂) ₂ CH ₃		MS m/z (M-H) ⁻ 291
99	—(CH ₂) ₂ CH ₃		MS m/z (M-H) ⁻ 295
100	—(CH ₂) ₂ CH ₃		MS m/z (M-H) ⁻ 298
101	—(CH ₂) ₂ CH ₃		MS m/z (M-H) ⁻ 259
102	—(CH ₂) ₂ CH ₃		MS m/z (M-H) ⁻ 302
103	—(CH ₂) ₂ CH ₃		MS m/z (M-H) ⁻ 303
104	—(CH ₂) ₂ CH ₃		MS m/z (M-H) ⁻ 305
105	—(CH ₂) ₂ CH ₃		MS m/z (M-H) ⁻ 313
106	—(CH ₂) ₂ CH ₃		MS m/z (M-H) ⁻ 321
107	—(CH ₂) ₂ CH ₃		MS m/z (M-H) ⁻ 297
108	—(CH ₂) ₂ CH ₃		MS m/z (M-H) ⁻ 333

Table 1-10



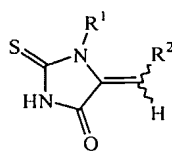
Cpd. No.	R¹	R²	Instrumental Data
109	—(CH₂)₂OCH₃		MS m/z (M-H)⁻ 305
110	—(CH₂)₂OCH₃		MS m/z (M-H)⁻ 307
111	—(CH₂)₂OCH₃		MS m/z (M-H)⁻ 311
112	—(CH₂)₂OCH₃		MS m/z (M-H)⁻ 314
113	—(CH₂)₂OCH₃		MS m/z (M-H)⁻ 275
114	—(CH₂)₂OCH₃		MS m/z (M-H)⁻ 318
115	—(CH₂)₂OCH₃		MS m/z (M-H)⁻ 319
116	—(CH₂)₂OCH₃		MS m/z (M-H)⁻ 321
117	—(CH₂)₂OCH₃		MS m/z (M-H)⁻ 329
118	—(CH₂)₂OCH₃		MS m/z (M-H)⁻ 337
119	—(CH₂)₂OCH₃		MS m/z (M-H)⁻ 313
120	—(CH₂)₂OCH₃		MS m/z (M-H)⁻ 349

Table 1-11



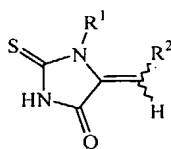
Cpd. No.	R¹	R²	Instrumental Data
121	$-(CH_2)_2-CH(CH_3)_2$		MS m/z (M-H)⁻ 317
122	$-(CH_2)_2-CH(CH_3)_2$		MS m/z (M-H)⁻ 319
123	$-(CH_2)_2-CH(CH_3)_2$		MS m/z (M-H)⁻ 323
124	$-(CH_2)_2-CH(CH_3)_2$		MS m/z (M-H)⁻ 326
125	$-(CH_2)_2-CH(CH_3)_2$		MS m/z (M-H)⁻ 287
126	$-(CH_2)_2-CH(CH_3)_2$		MS m/z (M-H)⁻ 330
127	$-(CH_2)_2-CH(CH_3)_2$		MS m/z (M-H)⁻ 331
128	$-(CH_2)_2-CH(CH_3)_2$		MS m/z (M-H)⁻ 333
129	$-(CH_2)_2-CH(CH_3)_2$		MS m/z (M-H)⁻ 341
130	$-(CH_2)_2-CH(CH_3)_2$		MS m/z (M-H)⁻ 349
131	$-(CH_2)_2-CH(CH_3)_2$		MS m/z (M-H)⁻ 325
132	$-(CH_2)_2-CH(CH_3)_2$		MS m/z (M-H)⁻ 361

Table 1-12



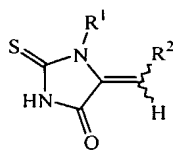
Cpd. No.	R ¹	R ²	Instrumental Data
133			MS m/z (M-H) ⁺ 357
134			MS m/z (M-H) ⁺ 359
135			MS m/z (M-H) ⁺ 363
136			MS m/z (M-H) ⁺ 366
137			MS m/z (M-H) ⁺ 327
138			MS m/z (M-H) ⁺ 370
139			MS m/z (M-H) ⁺ 371
140			MS m/z (M-H) ⁺ 373
141			MS m/z (M-H) ⁺ 381
142			MS m/z (M-H) ⁺ 389
143			MS m/z (M-H) ⁺ 365
144			MS m/z (M-H) ⁺ 401

Table 1-13



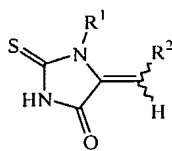
Cpd. No.	R ¹	R ²	Instrumental Data
145			MS m/z (M-H) ⁻ 337
146			MS m/z (M-H) ⁻ 339
147			MS m/z (M-H) ⁻ 343
148			MS m/z (M-H) ⁻ 346
149			MS m/z (M-H) ⁻ 307
150			MS m/z (M-H) ⁻ 350
151			MS m/z (M-H) ⁻ 351
152			MS m/z (M-H) ⁻ 353
153			MS m/z (M-H) ⁻ 361
154			MS m/z (M-H) ⁻ 369
155			MS m/z (M-H) ⁻ 345
156			MS m/z (M-H) ⁻ 381

Table 1-14



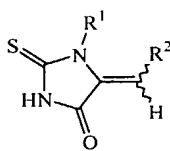
Cpd. No.	R¹	R²	Instrumental Data
157			MS m/z (M-H)⁻ 343
158			MS m/z (M-H)⁻ 345
159			MS m/z (M-H)⁻ 349
160			MS m/z (M-H)⁻ 352
161			MS m/z (M-H)⁻ 313
162			MS m/z (M-H)⁻ 356
163			MS m/z (M-H)⁻ 357
164			MS m/z (M-H)⁻ 359
165			MS m/z (M-H)⁻ 367
166			MS m/z (M-H)⁻ 375
167			MS m/z (M-H)⁻ 351
168			MS m/z (M-H)⁻ 387

Table 1-15



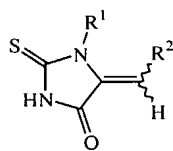
Cpd. No.	R¹	R²	Instrumental Data
169			MS m/z (M-H)⁻ 345
170			MS m/z (M-H)⁻ 347
171			MS m/z (M-H)⁻ 351
172			MS m/z (M-H)⁻ 354
173			MS m/z (M-H)⁻ 315
174			MS m/z (M-H)⁻ 358
175			MS m/z (M-H)⁻ 359
176			MS m/z (M-H)⁻ 361
177			MS m/z (M-H)⁻ 369
178			MS m/z (M-H)⁻ 377
179			MS m/z (M-H)⁻ 353
180			MS m/z (M-H)⁻ 389

Table 1-16



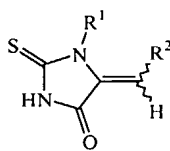
Cpd. No.	R ¹	R ²	Instrumental Data
181			MS m/z (M-H) ⁻ 371
182			MS m/z (M-H) ⁻ 373
183			MS m/z (M-H) ⁻ 377
184			MS m/z (M-H) ⁻ 380
185			MS m/z (M-H) ⁻ 341
186			MS m/z (M-H) ⁻ 384
187			MS m/z (M-H) ⁻ 385
188			MS m/z (M-H) ⁻ 387
189			MS m/z (M-H) ⁻ 395
190			MS m/z (M-H) ⁻ 403
191			MS m/z (M-H) ⁻ 379
192			MS m/z (M-H) ⁻ 415

Table 1-17



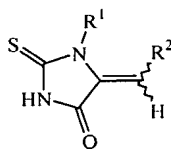
Cpd. No.	R ¹	R ²	Instrumental Data
193			MS m/z (M-H) ⁻ 271
194			MS m/z (M-H) ⁻ 277
195			MS m/z (M-H) ⁻ 296
196			MS m/z (M-H) ⁻ 272
197			MS m/z (M-H) ⁻ 301
198			MS m/z (M-H) ⁻ 327
199			MS m/z (M-H) ⁻ 289
200			MS m/z (M-H) ⁻ 331
201			MS m/z (M-H) ⁻ 313
202			MS m/z (M-H) ⁻ 315
203			MS m/z (M-H) ⁻ 363
204			MS m/z (M-H) ⁻ 407

Table 1-18



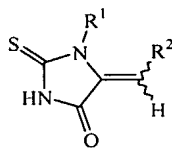
Cpd. No.	R ¹	R ²	Instrumental Data
205			MS m/z (M-H) ⁻ 257
206			MS m/z (M-H) ⁻ 263
207			MS m/z (M-H) ⁻ 282
208			MS m/z (M-H) ⁻ 258
209			MS m/z (M-H) ⁻ 287
210			MS m/z (M-H) ⁻ 313
211			MS m/z (M-H) ⁻ 275
212			MS m/z (M-H) ⁻ 317
213			MS m/z (M-H) ⁻ 299
214			MS m/z (M-H) ⁻ 301
215			MS m/z (M-H) ⁻ 349
216			MS m/z (M-H) ⁻ 393

Table 1-19



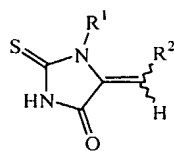
Cpd. No.	R¹	R²	Instrumental Data
217			MS m/z (M-H)⁻ 287
218			MS m/z (M-H)⁻ 293
219			MS m/z (M-H)⁻ 312
220			MS m/z (M-H)⁻ 288
221			MS m/z (M-H)⁻ 317
222			MS m/z (M-H)⁻ 343
223			MS m/z (M-H)⁻ 305
224			MS m/z (M-H)⁻ 347
225			MS m/z (M-H)⁻ 329
226			MS m/z (M-H)⁻ 331
227			MS m/z (M-H)⁻ 379
228			MS m/z (M-H)⁻ 423

Table 1-20



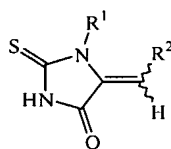
Cpd. No.	R ¹	R ²	Instrumental Data
229			MS m/z (M-H) ⁺ 297 ¹ H NMR: See Example
230			MS m/z (M-H) ⁺ 303
231			MS m/z (M-H) ⁺ 322
232			MS m/z (M-H) ⁺ 298
233			MS m/z (M-H) ⁺ 327
234			MS m/z (M-H) ⁺ 353
235			MS m/z (M-H) ⁺ 315
236			MS m/z (M-H) ⁺ 357
237			MS m/z (M-H) ⁺ 339
238			MS m/z (M-H) ⁺ 341
239			MS m/z (M-H) ⁺ 389
240			MS m/z (M-H) ⁺ 433

Table 1-21



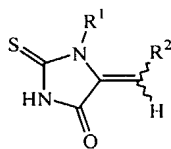
Cpd. No.	R¹	R²	Instrumental Data
241			MS m/z (M-H)⁻ 299
242			MS m/z (M-H)⁻ 305
243			MS m/z (M-H)⁻ 324
244			MS m/z (M-H)⁻ 300
245			MS m/z (M-H)⁻ 329
246			MS m/z (M-H)⁻ 355
247			MS m/z (M-H)⁻ 317
248			MS m/z (M-H)⁻ 359
249			MS m/z (M-H)⁻ 341
250			MS m/z (M-H)⁻ 343
251			MS m/z (M-H)⁻ 391
252			MS m/z (M-H)⁻ 435

Table 1-22



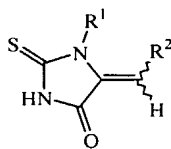
Cpd. No.	R ¹	R ²	Instrumental Data
253	—(CH ₂) ₂ SCH ₃		MS m/z (M-H) ⁻ 277
254	—(CH ₂) ₂ SCH ₃		MS m/z (M-H) ⁻ 283
255	—(CH ₂) ₂ SCH ₃		MS m/z (M-H) ⁻ 302
256	—(CH ₂) ₂ SCH ₃		MS m/z (M-H) ⁻ 278
257	—(CH ₂) ₂ SCH ₃		MS m/z (M-H) ⁻ 307
258	—(CH ₂) ₂ SCH ₃		MS m/z (M-H) ⁻ 333
259	—(CH ₂) ₂ SCH ₃		MS m/z (M-H) ⁻ 295
260	—(CH ₂) ₂ SCH ₃		MS m/z (M-H) ⁻ 337
261	—(CH ₂) ₂ SCH ₃		MS m/z (M-H) ⁻ 319
262	—(CH ₂) ₂ SCH ₃		MS m/z (M-H) ⁻ 321
263	—(CH ₂) ₂ SCH ₃		MS m/z (M-H) ⁻ 369
264	—(CH ₂) ₂ SCH ₃		MS m/z (M-H) ⁻ 413

Table 1-23



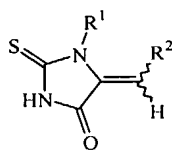
Cpd. No.	R ¹	R ²	Instrumental Data
265			MS m/z (M-H) ⁻ 307
266			MS m/z (M-H) ⁻ 313
267			MS m/z (M-H) ⁻ 332
268			MS m/z (M-H) ⁻ 308
269			MS m/z (M-H) ⁻ 337
270			MS m/z (M-H) ⁻ 363
271			MS m/z (M-H) ⁻ 325
272			MS m/z (M-H) ⁻ 367
273			MS m/z (M-H) ⁻ 349
274			MS m/z (M-H) ⁻ 351
275			MS m/z (M-H) ⁻ 399
276			MS m/z (M-H) ⁻ 443

Table 1-24



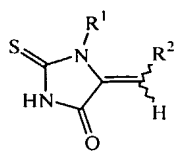
Cpd. No.	R ¹	R ²	Instrumental Data
277	—(CH ₂) ₂ O(CH ₂) ₂ OCH ₂ CH ₃		MS m/z (M-H) ⁻ 319
278	—(CH ₂) ₂ O(CH ₂) ₂ OCH ₂ CH ₃		MS m/z (M-H) ⁻ 325
279	—(CH ₂) ₂ O(CH ₂) ₂ OCH ₂ CH ₃		MS m/z (M-H) ⁻ 344
280	—(CH ₂) ₂ O(CH ₂) ₂ OCH ₂ CH ₃		MS m/z (M-H) ⁻ 320
281	—(CH ₂) ₂ O(CH ₂) ₂ OCH ₂ CH ₃		MS m/z (M-H) ⁻ 349
282	—(CH ₂) ₂ O(CH ₂) ₂ OCH ₂ CH ₃		MS m/z (M-H) ⁻ 375
283	—(CH ₂) ₂ O(CH ₂) ₂ OCH ₂ CH ₃		MS m/z (M-H) ⁻ 337
284	—(CH ₂) ₂ O(CH ₂) ₂ OCH ₂ CH ₃		MS m/z (M-H) ⁻ 379
285	—(CH ₂) ₂ O(CH ₂) ₂ OCH ₂ CH ₃		MS m/z (M-H) ⁻ 361
286	—(CH ₂) ₂ O(CH ₂) ₂ OCH ₂ CH ₃		MS m/z (M-H) ⁻ 363
287	—(CH ₂) ₂ O(CH ₂) ₂ OCH ₂ CH ₃		MS m/z (M-H) ⁻ 411
288	—(CH ₂) ₂ O(CH ₂) ₂ OCH ₂ CH ₃		MS m/z (M-H) ⁻ 455

Table 1-25



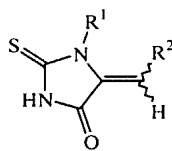
Cpd. No.	R¹	R²	Instrumental Data
289			MS m/z (M-H)⁻ 315
290			MS m/z (M-H)⁻ 317
291			MS m/z (M-H)⁻ 321
292			MS m/z (M-H)⁻ 324
293			MS m/z (M-H)⁻ 285
294			MS m/z (M-H)⁻ 328
295			MS m/z (M-H)⁻ 329
296			MS m/z (M-H)⁻ 331
297			MS m/z (M-H)⁻ 339
298			MS m/z (M-H)⁻ 347
299			MS m/z (M-H)⁻ 323
300			MS m/z (M-H)⁻ 359

Table 1-26



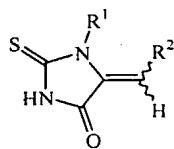
Cpd. No.	R¹	R²	Instrumental Data
301	—CH₂—	 H ₃ CH ₂ CO	MS m/z (M-H) ⁻ 301
302	—CH₂—	 —SCH ₃	MS m/z (M-H) ⁻ 303
303	—CH₂—		MS m/z (M-H) ⁻ 307
304	—CH₂—	 —N-CH ₃	MS m/z (M-H) ⁻ 310
305	—CH₂—	 H ₃ C	MS m/z (M-H) ⁻ 271
306	—CH₂—	 —NH—C(=O)—CH ₃	MS m/z (M-H) ⁻ 314
307	—CH₂—	 CH ₃ , OCH ₃ , H ₃ C	MS m/z (M-H) ⁻ 315
308	—CH₂—	 OCH ₃ , OCH ₃ , OCH ₃	MS m/z (M-H) ⁻ 317
309	—CH₂—	 —CF ₃	MS m/z (M-H) ⁻ 325
310	—CH₂—		MS m/z (M-H) ⁻ 333
311	—CH₂—	 F, Cl	MS m/z (M-H) ⁻ 309 ¹ H NMR: See Example
312	—CH₂—	 (H ₃ C) ₃ CS	MS m/z (M-H) ⁻ 345

Table 1-27



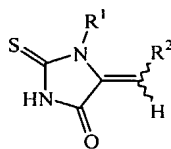
Cpd. No.	R ¹	R ²	Instrumental Data
313			MS m/z (M-H) ⁺ 331
314			MS m/z (M-H) ⁺ 333
315			MS m/z (M-H) ⁺ 337
316			MS m/z (M-H) ⁺ 340
317			MS m/z (M-H) ⁺ 301
318			MS m/z (M-H) ⁺ 344
319			MS m/z (M-H) ⁺ 345
320			MS m/z (M-H) ⁺ 347
321			MS m/z (M-H) ⁺ 355
322			MS m/z (M-H) ⁺ 363
323			MS m/z (M-H) ⁺ 339
324			MS m/z (M-H) ⁺ 375

Table 1-28



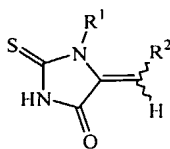
Cpd. No.	R ¹	R ²	Instrumental Data
325			MS m/z (M-H) ⁻ 341
326			MS m/z (M-H) ⁻ 343
327			MS m/z (M-H) ⁻ 347
328			MS m/z (M-H) ⁻ 350
329			MS m/z (M-H) ⁻ 311
330			MS m/z (M-H) ⁻ 354
331			MS m/z (M-H) ⁻ 355
332			MS m/z (M-H) ⁻ 357
333			MS m/z (M-H) ⁻ 365
334			MS m/z (M-H) ⁻ 373
335			MS m/z (M-H) ⁻ 349
336			MS m/z (M-H) ⁻ 385

Table 1-29



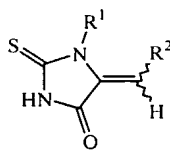
Cpd. No.	R ¹	R ²	Instrumental Data
337			MS m/z (M-H) ⁻ 343
338			MS m/z (M-H) ⁻ 345
339			MS m/z (M-H) ⁻ 349
340			MS m/z (M-H) ⁻ 352
341			MS m/z (M-H) ⁻ 313
342			MS m/z (M-H) ⁻ 356
343			MS m/z (M-H) ⁻ 357
344			MS m/z (M-H) ⁻ 359
345			MS m/z (M-H) ⁻ 367
346			MS m/z (M-H) ⁻ 375
347			MS m/z (M-H) ⁻ 351
348			MS m/z (M-H) ⁻ 387

Table 1-30



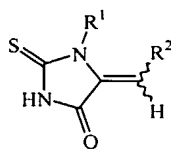
Cpd. No.	R¹	R²	Instrumental Data
349	—(CH₂)₂SCH₃		MS m/z (M-H)⁻ 321
350	—(CH₂)₂SCH₃		MS m/z (M-H)⁻ 323
351	—(CH₂)₂SCH₃		MS m/z (M-H)⁻ 327
352	—(CH₂)₂SCH₃		MS m/z (M-H)⁻ 330
353	—(CH₂)₂SCH₃		MS m/z (M-H)⁻ 291
354	—(CH₂)₂SCH₃		MS m/z (M-H)⁻ 334
355	—(CH₂)₂SCH₃		MS m/z (M-H)⁻ 335
356	—(CH₂)₂SCH₃		MS m/z (M-H)⁻ 337
357	—(CH₂)₂SCH₃		MS m/z (M-H)⁻ 345
358	—(CH₂)₂SCH₃		MS m/z (M-H)⁻ 353
359	—(CH₂)₂SCH₃		MS m/z (M-H)⁻ 329
360	—(CH₂)₂SCH₃		MS m/z (M-H)⁻ 365

Table 1-31



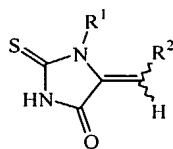
Cpd. No.	R ¹	R ²	Instrumental Data
361	—(CH ₂) ₂ —	H ₃ CH ₂ CO	MS m/z (M-H) ⁺ 351
362	—(CH ₂) ₂ —	——SCH ₃	MS m/z (M-H) ⁺ 353
363	—(CH ₂) ₂ —	—	MS m/z (M-H) ⁺ 357
364	—(CH ₂) ₂ —	—	MS m/z (M-H) ⁺ 360
365	—(CH ₂) ₂ —	—H ₃ C	MS m/z (M-H) ⁺ 321
366	—(CH ₂) ₂ —	—	MS m/z (M-H) ⁺ 364
367	—(CH ₂) ₂ —	—CH ₃ H ₃ C	MS m/z (M-H) ⁺ 365
368	—(CH ₂) ₂ —	—OCH ₃ OCH ₃	MS m/z (M-H) ⁺ 367
369	—(CH ₂) ₂ —	—CF ₃	MS m/z (M-H) ⁺ 375
370	—(CH ₂) ₂ —	—	MS m/z (M-H) ⁺ 383
371	—(CH ₂) ₂ —	—F Cl	MS m/z (M-H) ⁺ 359
372	—(CH ₂) ₂ —	—H ₃ C) ₃ CS	MS m/z (M-H) ⁺ 395

Table 1-32



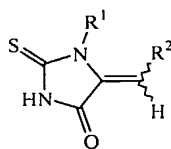
Cpd. No.	R ¹	R ²	Instrumental Data
373	—(CH ₂) ₂ O(CH ₂) ₂ OCH ₂ CH ₃		MS m/z (M-H) ⁻ 363
374	—(CH ₂) ₂ O(CH ₂) ₂ OCH ₂ CH ₃		MS m/z (M-H) ⁻ 365
375	—(CH ₂) ₂ O(CH ₂) ₂ OCH ₂ CH ₃		MS m/z (M-H) ⁻ 369
376	—(CH ₂) ₂ O(CH ₂) ₂ OCH ₂ CH ₃		MS m/z (M-H) ⁻ 372
377	—(CH ₂) ₂ O(CH ₂) ₂ OCH ₂ CH ₃		MS m/z (M-H) ⁻ 333
378	—(CH ₂) ₂ O(CH ₂) ₂ OCH ₂ CH ₃		MS m/z (M-H) ⁻ 376
379	—(CH ₂) ₂ O(CH ₂) ₂ OCH ₂ CH ₃		MS m/z (M-H) ⁻ 377
380	—(CH ₂) ₂ O(CH ₂) ₂ OCH ₂ CH ₃		MS m/z (M-H) ⁻ 379
381	—(CH ₂) ₂ O(CH ₂) ₂ OCH ₂ CH ₃		MS m/z (M-H) ⁻ 387
382	—(CH ₂) ₂ O(CH ₂) ₂ OCH ₂ CH ₃		MS m/z (M-H) ⁻ 395
383	—(CH ₂) ₂ O(CH ₂) ₂ OCH ₂ CH ₃		MS m/z (M-H) ⁻ 371 ¹ H NMR: See Example
384	—(CH ₂) ₂ O(CH ₂) ₂ OCH ₂ CH ₃		MS m/z (M-H) ⁻ 407

Table 1-33



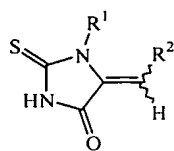
Cpd. No.	R ¹	R ²	Instrumental Data
385			MS m/z (M-H) ⁻ 337
386			MS m/z (M-H) ⁻ 343
387			MS m/z (M-H) ⁻ 362
388			MS m/z (M-H) ⁻ 338
389			MS m/z (M-H) ⁻ 367
390			MS m/z (M-H) ⁻ 393
391			MS m/z (M-H) ⁻ 355
392			MS m/z (M-H) ⁻ 397
393			MS m/z (M-H) ⁻ 379
394			MS m/z (M-H) ⁻ 381
395			MS m/z (M-H) ⁻ 429
396			MS m/z (M-H) ⁻ 473

Table 1-34



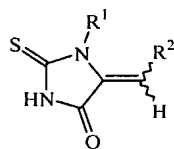
Cpd. No.	R¹	R²	Instrumental Data
397			MS m/z (M-H)⁻ 325
398			MS m/z (M-H)⁻ 331
399			MS m/z (M-H)⁻ 350
400			MS m/z (M-H)⁻ 326
401			MS m/z (M-H)⁻ 355
402			MS m/z (M-H)⁻ 381
403			MS m/z (M-H)⁻ 343
404			MS m/z (M-H)⁻ 385
405			MS m/z (M-H)⁻ 367
406			MS m/z (M-H)⁻ 369
407			MS m/z (M-H)⁻ 417
408			MS m/z (M-H)⁻ 461

Table 1-35



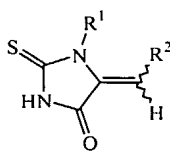
Cpd. No.	R ¹	R ²	Instrumental Data
409			MS m/z (M-H) ⁻ 321
410			MS m/z (M-H) ⁻ 327
411			MS m/z (M-H) ⁻ 346
412			MS m/z (M-H) ⁻ 322
413			MS m/z (M-H) ⁻ 351
414			MS m/z (M-H) ⁻ 377
415			MS m/z (M-H) ⁻ 339
416			MS m/z (M-H) ⁻ 381
417			MS m/z (M-H) ⁻ 363
418			MS m/z (M-H) ⁻ 365
419			MS m/z (M-H) ⁻ 413
420			MS m/z (M-H) ⁻ 457

Table 1-36



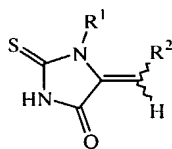
Cpd. No.	R ¹	R ²	Instrumental Data
421			MS m/z (M-H) ⁻ 365
422			MS m/z (M-H) ⁻ 371
423			MS m/z (M-H) ⁻ 390
424			MS m/z (M-H) ⁻ 366
425			MS m/z (M-H) ⁻ 395
426			MS m/z (M-H) ⁻ 421
427			MS m/z (M-H) ⁻ 383
428			MS m/z (M-H) ⁻ 425
429			MS m/z (M-H) ⁻ 407
430			MS m/z (M-H) ⁻ 409
431			MS m/z (M-H) ⁻ 457
432			MS m/z (M-H) ⁻ 501

Table 1-37



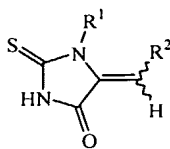
Cpd. No.	R ¹	R ²	Instrumental Data
433			MS m/z (M-H) ⁺ 341
434			MS m/z (M-H) ⁺ 347
435			MS m/z (M-H) ⁺ 366
436			MS m/z (M-H) ⁺ 342
437			MS m/z (M-H) ⁺ 371
438			MS m/z (M-H) ⁺ 397
439			MS m/z (M-H) ⁺ 359
440			MS m/z (M-H) ⁺ 401
441			MS m/z (M-H) ⁺ 383
442			MS m/z (M-H) ⁺ 385
443			MS m/z (M-H) ⁺ 433
444			MS m/z (M-H) ⁺ 477

Table 1-38



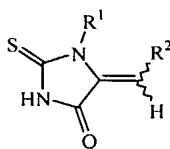
Cpd. No.	R ¹	R ²	Instrumental Data
445			MS m/z (M-H) ⁻ 351
446			MS m/z (M-H) ⁻ 357
447			MS m/z (M-H) ⁻ 376
448			MS m/z (M-H) ⁻ 352
449			MS m/z (M-H) ⁻ 381
450			MS m/z (M-H) ⁻ 407
451			MS m/z (M-H) ⁻ 369 ¹ H NMR: See Example
452			MS m/z (M-H) ⁻ 411
453			MS m/z (M-H) ⁻ 393
454			MS m/z (M-H) ⁻ 395
455			MS m/z (M-H) ⁻ 443
456			MS m/z (M-H) ⁻ 487

Table 1-39



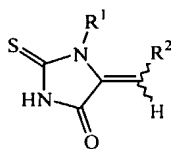
Cpd. No.	R ¹	R ²	Instrumental Data
457			MS m/z (M-H) ⁻ 383
458			MS m/z (M-H) ⁻ 389
459			MS m/z (M-H) ⁻ 408
460			MS m/z (M-H) ⁻ 384
461			MS m/z (M-H) ⁻ 413
462			MS m/z (M-H) ⁻ 439

Table 1-40



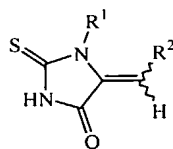
Cpd. No.	R ¹	R ²	Instrumental Data
463			MS m/z (M-H) ⁻ 401 ¹ H NMR: See Example
464			MS m/z (M-H) ⁻ 443
465			MS m/z (M-H) ⁻ 425
466			MS m/z (M-H) ⁻ 427
467			MS m/z (M-H) ⁻ 475
468			MS m/z (M-H) ⁻ 519

Table 1-41



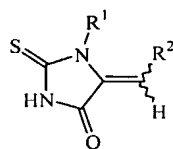
Cpd. No.	R¹	R²	Instrumental Data
469			MS m/z (M-H)⁻ 381
470			MS m/z (M-H)⁻ 383
471			MS m/z (M-H)⁻ 387
472			MS m/z (M-H)⁻ 390
473			MS m/z (M-H)⁻ 351
474			MS m/z (M-H)⁻ 394
475			MS m/z (M-H)⁻ 395
476			MS m/z (M-H)⁻ 397
477			MS m/z (M-H)⁻ 405
478			MS m/z (M-H)⁻ 413
479			MS m/z (M-H)⁻ 389
480			MS m/z (M-H)⁻ 425

Table 1-42



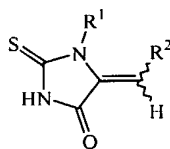
Cpd. No.	R ¹	R ²	Instrumental Data
481	—(CH ₂) ₂ —	 H ₃ CH ₂ CO	MS m/z (M-H) ⁻ 369
482	—(CH ₂) ₂ —	 —SCH ₃	MS m/z (M-H) ⁻ 371
483	—(CH ₂) ₂ —		MS m/z (M-H) ⁻ 375
484	—(CH ₂) ₂ —	 N-CH ₃	MS m/z (M-H) ⁻ 378
485	—(CH ₂) ₂ —	 H ₃ C	MS m/z (M-H) ⁻ 339
486	—(CH ₂) ₂ —	 —NH—C(=O)—CH ₃	MS m/z (M-H) ⁻ 382
487	—(CH ₂) ₂ —	 CH ₃ , OCH ₃ , H ₃ C	MS m/z (M-H) ⁻ 383
488	—(CH ₂) ₂ —	 OCH ₃ , OCH ₃ , OCH ₃	MS m/z (M-H) ⁻ 385
489	—(CH ₂) ₂ —	 —CF ₃	MS m/z (M-H) ⁻ 393
490	—(CH ₂) ₂ —		MS m/z (M-H) ⁻ 401
491	—(CH ₂) ₂ —	 F, Cl	MS m/z (M-H) ⁻ 377
492	—(CH ₂) ₂ —	 (H ₃ C) ₃ CS	MS m/z (M-H) ⁻ 413

Table 1-43



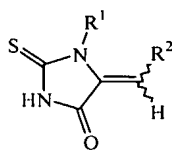
Cpd. No.	R ¹	R ²	Instrumental Data
493			MS m/z (M-H) ⁻ 365
494			MS m/z (M-H) ⁻ 367
495			MS m/z (M-H) ⁻ 371
496			MS m/z (M-H) ⁻ 374
497			MS m/z (M-H) ⁻ 335
498			MS m/z (M-H) ⁻ 378
499			MS m/z (M-H) ⁻ 379
500			MS m/z (M-H) ⁻ 381
501			MS m/z (M-H) ⁻ 389
502			MS m/z (M-H) ⁻ 397
503			MS m/z (M-H) ⁻ 373 ¹ H NMR: See Example
504			MS m/z (M-H) ⁻ 409

Table 1-44



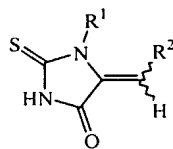
Cpd. No.	R ¹	R ²	Instrumental Data
505			MS m/z (M-H) ⁻ 409
506			MS m/z (M-H) ⁻ 411
507			MS m/z (M-H) ⁻ 415
508			MS m/z (M-H) ⁻ 418
509			MS m/z (M-H) ⁻ 379
510			MS m/z (M-H) ⁻ 422
511			MS m/z (M-H) ⁻ 423
512			MS m/z (M-H) ⁻ 425
513			MS m/z (M-H) ⁻ 433
514			MS m/z (M-H) ⁻ 441
515			MS m/z (M-H) ⁻ 417 ¹ H NMR: See Example
516			MS m/z (M-H) ⁻ 453

Table 1-45



Cpd. No.	R ¹	R ²	Instrumental Data
517			MS m/z (M-H) ⁻ 385
518			MS m/z (M-H) ⁻ 387
519			MS m/z (M-H) ⁻ 391
520			MS m/z (M-H) ⁻ 394
521			MS m/z (M-H) ⁻ 355
522			MS m/z (M-H) ⁻ 398
523			MS m/z (M-H) ⁻ 399
524			MS m/z (M-H) ⁻ 401
525			MS m/z (M-H) ⁻ 409
526			MS m/z (M-H) ⁻ 417
527			MS m/z (M-H) ⁻ 393
528			MS m/z (M-H) ⁻ 429

Table 1-46



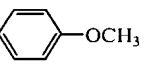
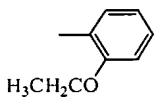
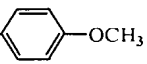
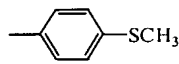
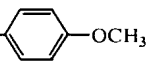
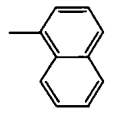
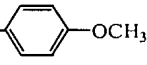
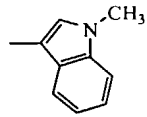
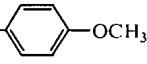
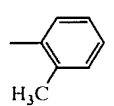
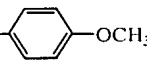
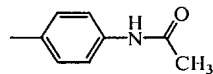
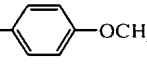
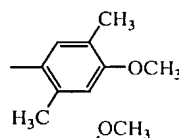
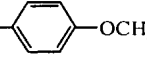
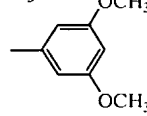
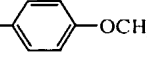
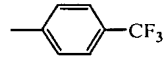
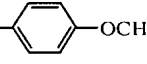
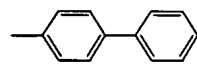
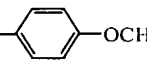
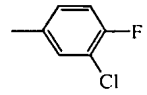
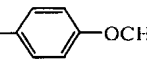
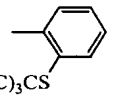
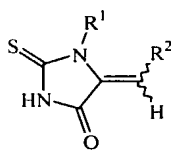
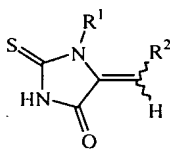
Cpd. No.	R¹	R²	Instrumental Data
529	—(CH₂)₃— 	 H₃CH₂CO	MS m/z (M-H)⁻ 395
530	—(CH₂)₃— 	—  —SCH₃	MS m/z (M-H)⁻ 397
531	—(CH₂)₃— 	—  —	MS m/z (M-H)⁻ 401
532	—(CH₂)₃— 	—  —N-CH₃	MS m/z (M-H)⁻ 404
533	—(CH₂)₃— 	—  — H₃C	MS m/z (M-H)⁻ 365
534	—(CH₂)₃— 	—  —NH-C(=O)CH₃	MS m/z (M-H)⁻ 408
535	—(CH₂)₃— 	—  — CH₃ H₃C	MS m/z (M-H)⁻ 409
536	—(CH₂)₃— 	—  — OCH₃ OCH₃	MS m/z (M-H)⁻ 411
537	—(CH₂)₃— 	—  —CF₃	MS m/z (M-H)⁻ 419
538	—(CH₂)₃— 	—  —	MS m/z (M-H)⁻ 427
539	—(CH₂)₃— 	—  — F Cl	MS m/z (M-H)⁻ 403
540	—(CH₂)₃— 	—  — (H₃C)₃CS	MS m/z (M-H)⁻ 439

Table 1-47



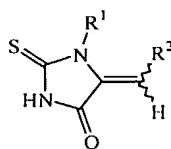
Cpd. No.	R ¹	R ²	Instrumental Data
541			MS m/z (M-H) ⁻ 427
542			MS m/z (M-H) ⁻ 429
543			MS m/z (M-H) ⁻ 433
544			MS m/z (M-H) ⁻ 436
545			MS m/z (M-H) ⁻ 397
546			MS m/z (M-H) ⁻ 440

Table 1-48



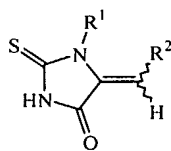
Cpd. No.	R ¹	R ²	Instrumental Data
547			MS m/z (M-H) ⁻ 441
548			MS m/z (M-H) ⁻ 443
549			MS m/z (M-H) ⁻ 451
550			MS m/z (M-H) ⁻ 459
551			MS m/z (M-H) ⁻ 435
552			MS m/z (M-H) ⁻ 471

Table 1-49



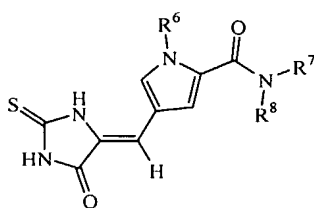
Cpd. No.	R ¹	R ²	Instrumental Data
553	—(CH ₂) ₂ CH ₃		MS m/z (M-H) ⁻ 235
554	—(CH ₂) ₂ OCH ₃		MS m/z (M-H) ⁻ 251
555	—(CH ₂) ₂ CH ₃ CH ₃		MS m/z (M-H) ⁻ 263
556	—(CH ₂) ₂ —		MS m/z (M-H) ⁻ 303
557	—CH ₂ —		MS m/z (M-H) ⁻ 283
558	—CH ₂ —		MS m/z (M-H) ⁻ 289
559	—CH ₂ —		MS m/z (M-H) ⁻ 291
560	—CH ₂ —		MS m/z (M-H) ⁻ 317
561			MS m/z (M-H) ⁻ 261
562	—CH ₂ —		MS m/z (M-H) ⁻ 247
563	—CH ₂ —		MS m/z (M-H) ⁻ 277
564	—CH ₂ —		MS m/z (M-H) ⁻ 287

Table 1-50



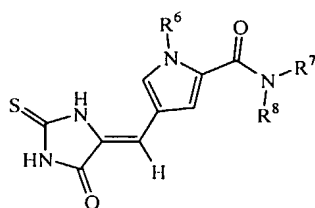
Cpd. No.	R ¹	R ²	Instrumental Data
565			MS m/z (M-H) ⁻ 289
566			MS m/z (M-H) ⁻ 267
567			MS m/z (M-H) ⁻ 297
568			MS m/z (M-H) ⁻ 309
569			MS m/z (M-H) ⁻ 327
570			MS m/z (M-H) ⁻ 315
571			MS m/z (M-H) ⁻ 311
572			MS m/z (M-H) ⁻ 355
573			MS m/z (M-H) ⁻ 331
574			MS m/z (M-H) ⁻ 341
575			MS m/z (M-H) ⁻ 373

Table 2-1



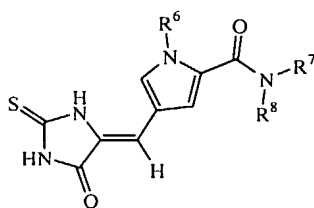
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
576			MS m/z (M-H) ⁺ 367
577			MS m/z (M-H) ⁺ 395
578			MS m/z (M-H) ⁺ 397
579			MS m/z (M-H) ⁺ 405
580			MS m/z (M-H) ⁺ 429
581			MS m/z (M-H) ⁺ 435
582			MS m/z (M-H) ⁺ 443
583			MS m/z (M-H) ⁺ 449
584			MS m/z (M-H) ⁺ 459
585			MS m/z (M-H) ⁺ 465
586			MS m/z (M-H) ⁺ 475
587			MS m/z (M-H) ⁺ 483

Table 2-2



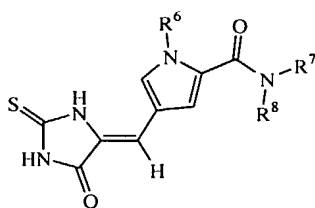
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
588			MS m/z (M-H) ⁻ 435
589			MS m/z (M-H) ⁻ 463
590			MS m/z (M-H) ⁻ 465
591			MS m/z (M-H) ⁻ 473
592			MS m/z (M-H) ⁻ 497
593			MS m/z (M-H) ⁻ 503
594			MS m/z (M-H) ⁻ 511
595			MS m/z (M-H) ⁻ 517
596			MS m/z (M-H) ⁻ 527
597			MS m/z (M-H) ⁻ 533
598			MS m/z (M-H) ⁻ 543
599			MS m/z (M-H) ⁻ 551

Table 2-3



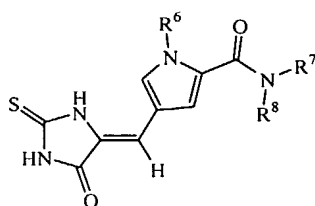
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
600			MS m/z (M-H) ⁻ 423
601			MS m/z (M-H) ⁻ 451
602			MS m/z (M-H) ⁻ 453
603			MS m/z (M-H) ⁻ 461
604			MS m/z (M-H) ⁻ 485
605			MS m/z (M-H) ⁻ 491
606			MS m/z (M-H) ⁻ 499
607			MS m/z (M-H) ⁻ 505
608			MS m/z (M-H) ⁻ 515
609			MS m/z (M-H) ⁻ 521
610			MS m/z (M-H) ⁻ 531
611			MS m/z (M-H) ⁻ 539

Table 2-4



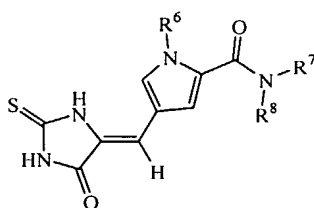
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
612			MS m/z (M-H) ⁻ 392
613			MS m/z (M-H) ⁻ 420
614			MS m/z (M-H) ⁻ 422
615			MS m/z (M-H) ⁻ 430
616			MS m/z (M-H) ⁻ 454
617			MS m/z (M-H) ⁻ 460
618			MS m/z (M-H) ⁻ 468
619			MS m/z (M-H) ⁻ 474
620			MS m/z (M-H) ⁻ 484
621			MS m/z (M-H) ⁻ 490
622			MS m/z (M-H) ⁺ 500
623			MS m/z (M-H) ⁻ 508

Table 2-5



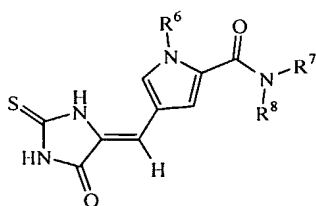
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
624			MS m/z (M-H) ⁻ 521
625			MS m/z (M-H) ⁻ 550
626			MS m/z (M-H) ⁻ 551
627			MS m/z (M-H) ⁻ 559
628			MS m/z (M-H) ⁻ 583
629			MS m/z (M-H) ⁻ 589
630			MS m/z (M-H) ⁻ 597
631			MS m/z (M-H) ⁻ 603
632			MS m/z (M-H) ⁻ 613
633			MS m/z (M-H) ⁻ 619
634			MS m/z (M-H) ⁻ 629
635			MS m/z (M-H) ⁻ 637

Table 2-6



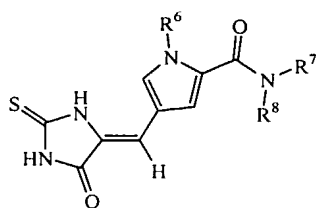
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
636			MS m/z (M-H) ⁻ 443
637			MS m/z (M-H) ⁻ 471
638			MS m/z (M-H) ⁻ 473
639			MS m/z (M-H) ⁻ 481
640			MS m/z (M-H) ⁻ 505
641			MS m/z (M-H) ⁻ 511
642			MS m/z (M-H) ⁻ 519
643			MS m/z (M-H) ⁻ 525
644			MS m/z (M-H) ⁻ 535
645			MS m/z (M-H) ⁻ 541
646			MS m/z (M-H) ⁻ 551
647			MS m/z (M-H) ⁻ 559

Table 2-7



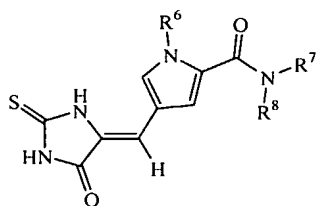
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
648			MS m/z (M-H) ⁻ 381
649			MS m/z (M-H) ⁻ 409
650			MS m/z (M-H) ⁻ 411
651			MS m/z (M-H) ⁻ 419
652			MS m/z (M-H) ⁻ 443
653			MS m/z (M-H) ⁻ 449
654			MS m/z (M-H) ⁻ 457
655			MS m/z (M-H) ⁻ 463
656			MS m/z (M-H) ⁻ 473
657			MS m/z (M-H) ⁻ 479
658			MS m/z (M-H) ⁻ 489
659			MS m/z (M-H) ⁻ 497

Table 2-8



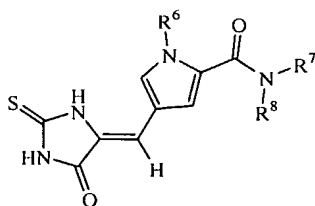
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
660			MS m/z (M-H) ⁻ 417
661			MS m/z (M-H) ⁻ 445
662			MS m/z (M-H) ⁻ 447
663			MS m/z (M-H) ⁻ 455
664			MS m/z (M-H) ⁻ 479
665			MS m/z (M-H) ⁻ 485
666			MS m/z (M-H) ⁻ 493
667			MS m/z (M-H) ⁻ 499
668			MS m/z (M-H) ⁻ 509
669			MS m/z (M-H) ⁻ 515
670			MS m/z (M-H) ⁻ 525
671			MS m/z (M-H) ⁻ 533

Table 2-9



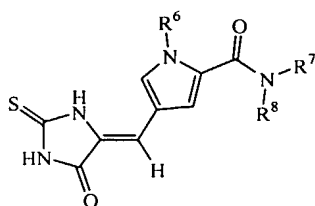
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
672			MS m/z (M-H) ⁻ 395
673			MS m/z (M-H) ⁻ 447
674			MS m/z (M-H) ⁻ 450
675			MS m/z (M-H) ⁻ 519
676			MS m/z (M-H) ⁻ 379
677			MS m/z (M-H) ⁻ 409
678			MS m/z (M-H) ⁻ 421
679			MS m/z (M-H) ⁻ 459
680			MS m/z (M-H) ⁻ 461
681			MS m/z (M-H) ⁻ 475
682			MS m/z (M-H) ⁻ 429
683			MS m/z (M-H) ⁻ 383

Table 2-10



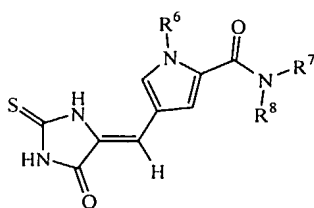
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
684			MS m/z (M-H) ⁻ 463
685			MS m/z (M-H) ⁻ 515
686			MS m/z (M-H) ⁻ 518
687			MS m/z (M-H) ⁻ 587
688			MS m/z (M-H) ⁻ 447
689			MS m/z (M-H) ⁻ 477
690			MS m/z (M-H) ⁻ 489
691			MS m/z (M-H) ⁻ 527
692			MS m/z (M-H) ⁻ 529
693			MS m/z (M-H) ⁻ 543
694			MS m/z (M-H) ⁻ 497
695			MS m/z (M-H) ⁻ 451

Table 2-11



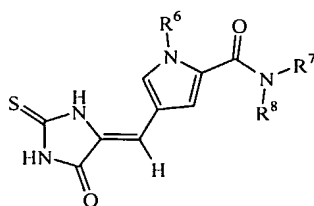
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
696			MS m/z (M-H) ⁻ 451
697			MS m/z (M-H) ⁻ 503
698			MS m/z (M-H) ⁻ 506
699			MS m/z (M-H) ⁻ 575
700			MS m/z (M-H) ⁻ 435
701			MS m/z (M-H) ⁻ 465
702			MS m/z (M-H) ⁻ 477
703			MS m/z (M-H) ⁻ 515
704			MS m/z (M-H) ⁻ 517
705			MS m/z (M-H) ⁻ 531
706			MS m/z (M-H) ⁻ 487
707			MS m/z (M-H) ⁻ 439

Table 2-12



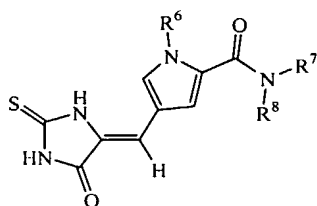
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
708			MS m/z (M-H) ⁻ 420
709			MS m/z (M-H) ⁻ 472
710			MS m/z (M-H) ⁻ 475
711			MS m/z (M-H) ⁻ 544
712			MS m/z (M-H) ⁻ 404
713			MS m/z (M-H) ⁻ 434
714			MS m/z (M-H) ⁻ 446
715			MS m/z (M-H) ⁻ 484
716			MS m/z (M-H) ⁻ 486
717			MS m/z (M-H) ⁻ 500
718			MS m/z (M-H) ⁺ 454
719			MS m/z (M-H) ⁻ 408

Table 2-13



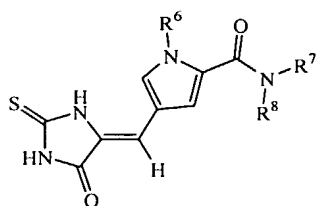
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
720			MS m/z (M-H) ⁺ 549
721			MS m/z (M-H) ⁺ 601
722			MS m/z (M-H) ⁺ 604
723			MS m/z (M-H) ⁺ 673
724			MS m/z (M-H) ⁺ 533
725			MS m/z (M-H) ⁺ 563
726			MS m/z (M-H) ⁺ 575
727			MS m/z (M-H) ⁺ 613
728			MS m/z (M-H) ⁺ 615
729			MS m/z (M-H) ⁺ 629
730			MS m/z (M-H) ⁺ 583
731			MS m/z (M-H) ⁺ 537

Table 2-14



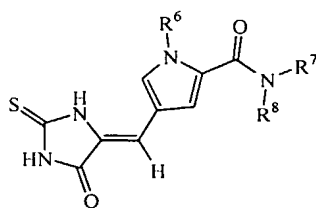
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
732			MS m/z (M-H) ⁻ 471
733			MS m/z (M-H) ⁻ 523
734			MS m/z (M-H) ⁻ 526
735			MS m/z (M-H) ⁻ 595
736			MS m/z (M-H) ⁻ 455
737			MS m/z (M-H) ⁻ 485
738			MS m/z (M-H) ⁻ 497
739			MS m/z (M-H) ⁻ 535
740			MS m/z (M-H) ⁻ 537
741			MS m/z (M-H) ⁻ 551
742			MS m/z (M-H) ⁻ 505
743			MS m/z (M-H) ⁻ 459

Table 2-15



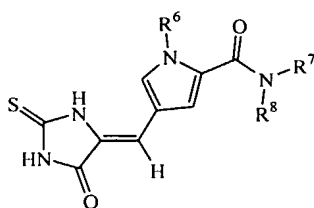
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
744			MS m/z (M-H) ⁻ 409
745			MS m/z (M-H) ⁻ 461
746			MS m/z (M-H) ⁻ 464
747			MS m/z (M-H) ⁻ 533
748			MS m/z (M-H) ⁻ 393
749			MS m/z (M-H) ⁻ 423
750			MS m/z (M-H) ⁻ 435
751			MS m/z (M-H) ⁻ 473
752			MS m/z (M-H) ⁻ 475
753			MS m/z (M-H) ⁻ 489
754			MS m/z (M-H) ⁻ 443
755			MS m/z (M-H) ⁻ 397

Table 2-16



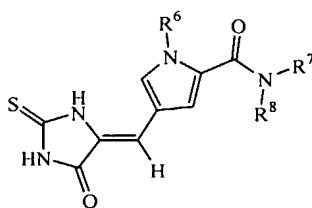
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
756			MS m/z (M-H) ⁺ 445
757			MS m/z (M-H) ⁺ 497
758			MS m/z (M-H) ⁺ 500
759			MS m/z (M-H) ⁺ 569
760			MS m/z (M-H) ⁺ 429
761			MS m/z (M-H) ⁺ 459
762			MS m/z (M-H) ⁺ 471
763			MS m/z (M-H) ⁺ 509
764			MS m/z (M-H) ⁺ 511
765			MS m/z (M-H) ⁺ 525
766			MS m/z (M-H) ⁺ 479
767			MS m/z (M-H) ⁺ 433

Table 2-17



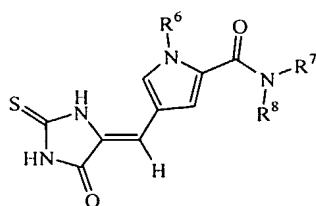
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
768			MS m/z (M-H) ⁺ 391
769			MS m/z (M-H) ⁺ 491
770			MS m/z (M-H) ⁺ 392
771			MS m/z (M-H) ⁺ 423
772			MS m/z (M-H) ⁺ 421
773			MS m/z (M-H) ⁺ 471
774			MS m/z (M-H) ⁺ 465
775			MS m/z (M-H) ⁺ 483
776			MS m/z (M-H) ⁺ 488
777			MS m/z (M-H) ⁺ 436
778			MS m/z (M-H) ⁺ 488
779			MS m/z (M-H) ⁺ 441

Table 2-18



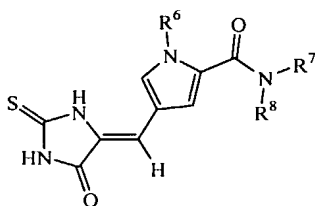
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
780			MS m/z (M-H) ⁺ 459
781			MS m/z (M-H) ⁺ 559
782			MS m/z (M-H) ⁺ 460
783			MS m/z (M-H) ⁺ 491
784			MS m/z (M-H) ⁺ 489
785			MS m/z (M-H) ⁺ 539
786			MS m/z (M-H) ⁺ 533
787			MS m/z (M-H) ⁺ 551
788			MS m/z (M-H) ⁺ 556
789			MS m/z (M-H) ⁺ 504
790			MS m/z (M-H) ⁺ 556
791			MS m/z (M-H) ⁺ 509

Table 2-19



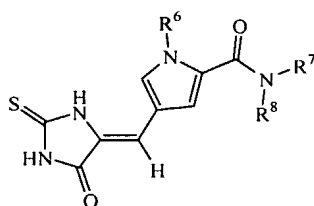
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
792			MS m/z (M-H) ⁻ 447
793			MS m/z (M-H) ⁻ 547
794			MS m/z (M-H) ⁻ 448
795			MS m/z (M-H) ⁻ 479
796			MS m/z (M-H) ⁻ 477
797			MS m/z (M-H) ⁻ 527
798			MS m/z (M-H) ⁻ 522
799			MS m/z (M-H) ⁻ 539
800			MS m/z (M-H) ⁻ 544
801			MS m/z (M-H) ⁻ 492
802			MS m/z (M-H) ⁻ 544
803			MS m/z (M-H) ⁻ 497

Table 2-20



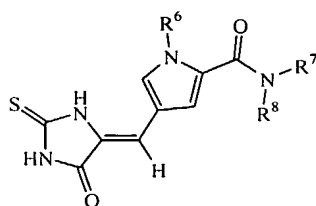
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
804			MS m/z (M-H) ⁻ 416
805			MS m/z (M-H) ⁻ 516
806			MS m/z (M-H) ⁻ 417
807			MS m/z (M-H) ⁻ 448
808			MS m/z (M-H) ⁻ 446
809			MS m/z (M-H) ⁻ 496
810			MS m/z (M-H) ⁻ 490
811			MS m/z (M-H) ⁻ 508
812			MS m/z (M-H) ⁻ 513
813			MS m/z (M-H) ⁻ 461
814			MS m/z (M-H) ⁻ 513
815			MS m/z (M-H) ⁻ 466

Table 2-21



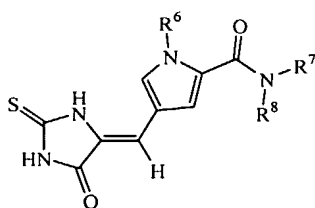
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
816			MS m/z (M-H) ⁺ 545
817			MS m/z (M-H) ⁺ 645
818			MS m/z (M-H) ⁺ 546
819			MS m/z (M-H) ⁺ 577
820			MS m/z (M-H) ⁺ 575
821			MS m/z (M-H) ⁺ 625
822			MS m/z (M-H) ⁺ 619
823			MS m/z (M-H) ⁺ 637
824			MS m/z (M-H) ⁺ 642
825			MS m/z (M-H) ⁺ 590
826			MS m/z (M-H) ⁺ 642
827			MS m/z (M-H) ⁺ 595

Table 2-22



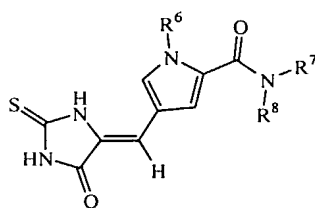
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
828			MS m/z (M-H) ⁺ 467
829			MS m/z (M-H) ⁺ 567
830			MS m/z (M-H) ⁺ 468
831			MS m/z (M-H) ⁺ 499
832			MS m/z (M-H) ⁺ 497
833			MS m/z (M-H) ⁺ 547
834			MS m/z (M-H) ⁺ 541
835			MS m/z (M-H) ⁺ 559
836			MS m/z (M-H) ⁺ 564
837			MS m/z (M-H) ⁺ 512
838			MS m/z (M-H) ⁺ 564
839			MS m/z (M-H) ⁺ 517

Table 2-23



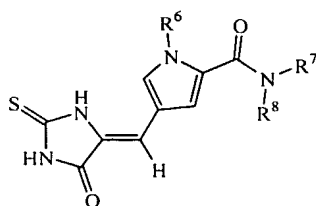
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
840			MS m/z (M-H) ⁻ 405
841			MS m/z (M-H) ⁻ 505
842			MS m/z (M-H) ⁻ 406
843			MS m/z (M-H) ⁻ 437
844			MS m/z (M-H) ⁻ 435
845			MS m/z (M-H) ⁻ 485
846			MS m/z (M-H) ⁻ 479
847			MS m/z (M-H) ⁻ 497
848			MS m/z (M-H) ⁻ 502
849			MS m/z (M-H) ⁻ 450
850			MS m/z (M-H) ⁻ 502
851			MS m/z (M-H) ⁻ 455

Table 2-24



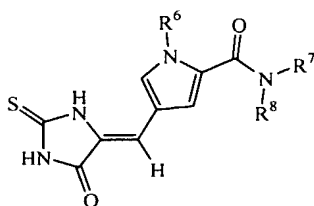
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
852			MS m/z (M-H) ⁺ 441
853			MS m/z (M-H) ⁺ 541
854			MS m/z (M-H) ⁺ 442
855			MS m/z (M-H) ⁺ 473
856			MS m/z (M-H) ⁺ 471
857			MS m/z (M-H) ⁺ 521
858			MS m/z (M-H) ⁺ 515
859			MS m/z (M-H) ⁺ 533
860			MS m/z (M-H) ⁺ 538
861			MS m/z (M-H) ⁺ 486
862			MS m/z (M-H) ⁺ 538
863			MS m/z (M-H) ⁺ 491

Table 2-25



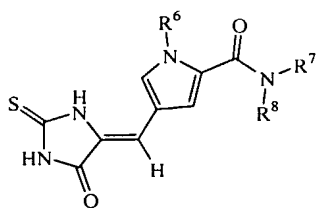
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
864			MS m/z (M-H) ⁻ 401
865			MS m/z (M-H) ⁻ 429
866			MS m/z (M-H) ⁻ 431
867			MS m/z (M-H) ⁻ 439
868			MS m/z (M-H) ⁻ 463
869			MS m/z (M-H) ⁻ 469
870			MS m/z (M-H) ⁻ 477
871			MS m/z (M-H) ⁻ 483
872			MS m/z (M-H) ⁻ 493
873			MS m/z (M-H) ⁻ 499
874			MS m/z (M-H) ⁻ 509
875			MS m/z (M-H) ⁻ 517

Table 2-26



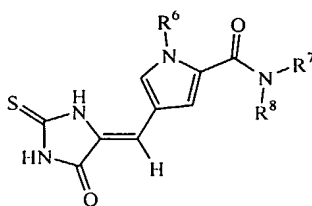
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
876			MS m/z (M-H) ⁺ 385
877			MS m/z (M-H) ⁺ 413
878			MS m/z (M-H) ⁺ 415
879			MS m/z (M-H) ⁺ 423
880			MS m/z (M-H) ⁺ 447
881			MS m/z (M-H) ⁺ 453
882			MS m/z (M-H) ⁺ 461
883			MS m/z (M-H) ⁺ 467
884			MS m/z (M-H) ⁺ 477
885			MS m/z (M-H) ⁺ 483
886			MS m/z (M-H) ⁺ 493
887			MS m/z (M-H) ⁺ 501

Table 2-27



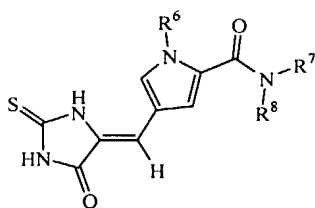
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
888			MS m/z (M-H) ⁻ 425
889			MS m/z (M-H) ⁻ 453
890			MS m/z (M-H) ⁻ 455
891			MS m/z (M-H) ⁻ 463
892			MS m/z (M-H) ⁻ 487
893			MS m/z (M-H) ⁻ 493
894			MS m/z (M-H) ⁻ 501
895			MS m/z (M-H) ⁻ 507
896			MS m/z (M-H) ⁻ 517
897			MS m/z (M-H) ⁻ 523
898			MS m/z (M-H) ⁻ 533
899			MS m/z (M-H) ⁻ 541

Table 2-28



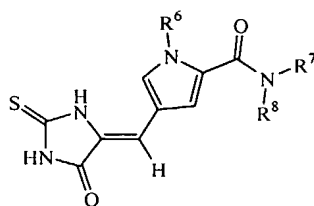
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
900			MS m/z (M-H) ⁺ 445
901			MS m/z (M-H) ⁺ 473
902			MS m/z (M-H) ⁺ 475
903			MS m/z (M-H) ⁺ 483
904			MS m/z (M-H) ⁺ 507
905			MS m/z (M-H) ⁺ 513
906			MS m/z (M-H) ⁺ 521
907			MS m/z (M-H) ⁺ 527
908			MS m/z (M-H) ⁺ 537
909			MS m/z (M-H) ⁺ 543
910			MS m/z (M-H) ⁺ 553
911			MS m/z (M-H) ⁺ 561

Table 2-29



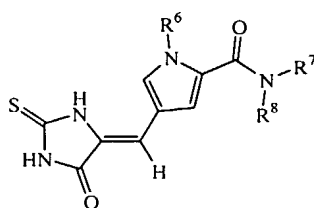
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
912			MS m/z (M-H) ⁻ 381
913			MS m/z (M-H) ⁻ 409
914			MS m/z (M-H) ⁻ 411
915			MS m/z (M-H) ⁻ 419
916			MS m/z (M-H) ⁻ 443
917			MS m/z (M-H) ⁻ 449
918			MS m/z (M-H) ⁻ 457
919			MS m/z (M-H) ⁻ 463
920			MS m/z (M-H) ⁻ 473
921			MS m/z (M-H) ⁻ 479
922			MS m/z (M-H) ⁻ 489
923			MS m/z (M-H) ⁻ 497

Table 2-30



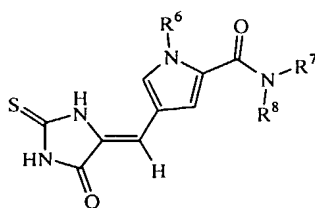
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
924			MS m/z (M-H) ⁻ 435
925			MS m/z (M-H) ⁻ 463
926			MS m/z (M-H) ⁻ 465
927			MS m/z (M-H) ⁻ 473
928			MS m/z (M-H) ⁻ 497
929			MS m/z (M-H) ⁻ 503
930			MS m/z (M-H) ⁻ 511
931			MS m/z (M-H) ⁻ 517
932			MS m/z (M-H) ⁻ 527
933			MS m/z (M-H) ⁻ 833
934			MS m/z (M-H) ⁻ 543
935			MS m/z (M-H) ⁻ 551

Table 2-31



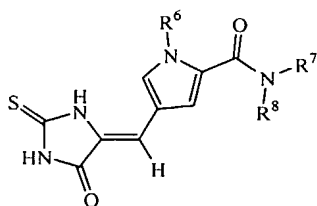
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
936			MS m/z (M-H) ⁻ 397
937			MS m/z (M-H) ⁻ 425
938			MS m/z (M-H) ⁻ 427
939			MS m/z (M-H) ⁻ 435
940			MS m/z (M-H) ⁻ 459
941			MS m/z (M-H) ⁻ 465
942			MS m/z (M-H) ⁻ 473
943			MS m/z (M-H) ⁻ 479
944			MS m/z (M-H) ⁻ 489
945			MS m/z (M-H) ⁻ 495
946			MS m/z (M-H) ⁻ 505
947			MS m/z (M-H) ⁻ 513

Table 2-32



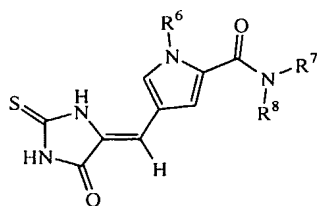
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
948			MS m/z (M-H) ⁻ 392
949			MS m/z (M-H) ⁻ 420
950			MS m/z (M-H) ⁻ 422
951			MS m/z (M-H) ⁻ 430
952			MS m/z (M-H) ⁻ 454
953			MS m/z (M-H) ⁻ 460
954			MS m/z (M-H) ⁻ 468
955			MS m/z (M-H) ⁻ 474
956			MS m/z (M-H) ⁻ 484
957			MS m/z (M-H) ⁻ 490
958			MS m/z (M-H) ⁻ 500
959			MS m/z (M-H) ⁻ 508

Table 2-33



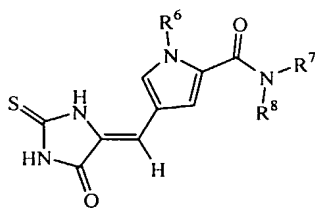
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
960		$\text{—N—CH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$	MS m/z (M-H) ⁺ 429
961		$\text{—N—(CH}_2)_2\text{—}$	MS m/z (M-H) ⁺ 481
962		$\text{—N—(CH}_2)_3\text{—N—}$	MS m/z (M-H) ⁺ 484
963		$\text{—N—(CH}_2)_2\text{—}$	MS m/z (M-H) ⁺ 553
964		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 413
965		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 443
966		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 455
967		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 493
968		$\text{—N—CH}_2\text{CHC}(\text{CH}_3)(\text{CH}_2)_2\text{CHC}(\text{CH}_3)_2$	MS m/z (M-H) ⁺ 495
969		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 509
970		$\text{—N—(CH}_2)_2\text{—}$	MS m/z (M-H) ⁺ 463
971		$\text{—N—(CH}_2)_2\text{—OH}$	MS m/z (M-H) ⁺ 417

Table 2-34



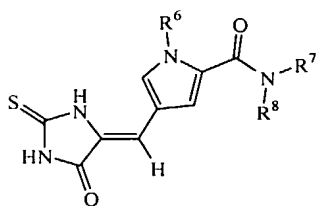
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
972		$\text{—N—CH}_2\text{CH(CH}_3\text{)CH}_2\text{CH}_3$	MS m/z (M-H) ⁺ 413
973		$\text{—N—(CH}_2\text{)}_2\text{—}$	MS m/z (M-H) ⁺ 465
974		$\text{—N—(CH}_2\text{)}_3\text{—N—}$	MS m/z (M-H) ⁺ 468
975		$\text{—N—(CH}_2\text{)}_2\text{—}$	MS m/z (M-H) ⁺ 537
976		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 397
977		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 427
978		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 439
979		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 477
980		$\text{—N—CH}_2\text{CHC(CH}_3\text{)(CH}_2\text{)}_2\text{CHC(CH}_3\text{)}_2$	MS m/z (M-H) ⁺ 479
981		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 493
982		$\text{—N—(CH}_2\text{)}_2\text{—}$	MS m/z (M-H) ⁺ 447
983		$\text{—N—(CH}_2\text{)}_2\text{—OH}$	MS m/z (M-H) ⁺ 401

Table 2-35



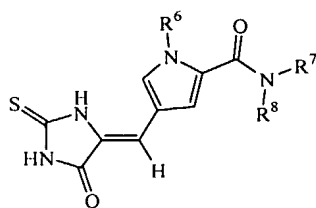
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
984			MS m/z (M-H) ⁺ 453
985			MS m/z (M-H) ⁺ 505
986			MS m/z (M-H) ⁺ 508
987			MS m/z (M-H) ⁺ 577
988			MS m/z (M-H) ⁺ 437
989			MS m/z (M-H) ⁺ 467
990			MS m/z (M-H) ⁺ 479
991			MS m/z (M-H) ⁺ 517
992			MS m/z (M-H) ⁺ 519
993			MS m/z (M-H) ⁺ 533
994			MS m/z (M-H) ⁺ 487
995			MS m/z (M-H) ⁺ 441

Table 2-36



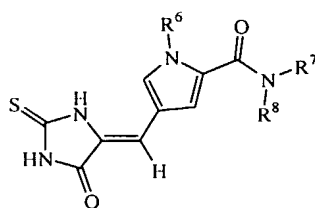
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
996			MS m/z (M-H) ⁻ 473
997			MS m/z (M-H) ⁻ 525
998			MS m/z (M-H) ⁻ 528
999			MS m/z (M-H) ⁻ 597
1000			MS m/z (M-H) ⁻ 457
1001			MS m/z (M-H) ⁻ 487
1002			MS m/z (M-H) ⁻ 499
1003			MS m/z (M-H) ⁻ 537
1004			MS m/z (M-H) ⁻ 539
1005			MS m/z (M-H) ⁻ 553
1006			MS m/z (M-H) ⁻ 507
1007			MS m/z (M-H) ⁻ 461

Table 2-37



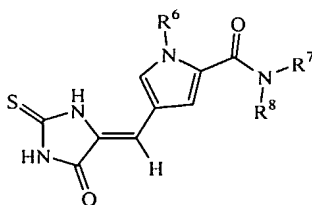
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1008			MS m/z (M-H) ⁺ 409
1009			MS m/z (M-H) ⁺ 461
1010			MS m/z (M-H) ⁺ 464
1011			MS m/z (M-H) ⁺ 533
1012			MS m/z (M-H) ⁺ 393
1013			MS m/z (M-H) ⁺ 423
1014			MS m/z (M-H) ⁺ 435
1015			MS m/z (M-H) ⁺ 473
1016			MS m/z (M-H) ⁺ 475
1017			MS m/z (M-H) ⁺ 489
1018			MS m/z (M-H) ⁺ 443
1019			MS m/z (M-H) ⁺ 397

Table 2-38



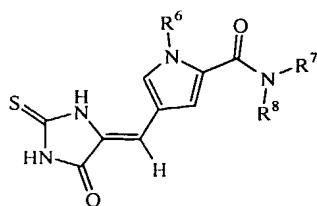
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1020			MS m/z (M-H) ⁺ 463
1021			MS m/z (M-H) ⁺ 515
1022			MS m/z (M-H) ⁺ 518
1023			MS m/z (M-H) ⁺ 587
1024			MS m/z (M-H) ⁺ 447
1025			MS m/z (M-H) ⁺ 477
1026			MS m/z (M-H) ⁺ 489
1027			MS m/z (M-H) ⁺ 527
1028			MS m/z (M-H) ⁺ 529
1029			MS m/z (M-H) ⁺ 543
1030			MS m/z (M-H) ⁺ 497
1031			MS m/z (M-H) ⁺ 451

Table 2-39



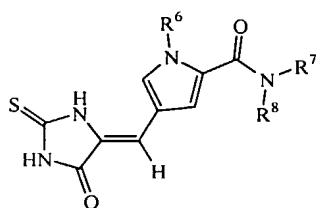
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1032			MS m/z (M-H) ⁻ 425
1033			MS m/z (M-H) ⁻ 477
1034			MS m/z (M-H) ⁻ 480
1035			MS m/z (M-H) ⁻ 549
1036			MS m/z (M-H) ⁻ 409
1037			MS m/z (M-H) ⁻ 439
1038			MS m/z (M-H) ⁻ 451
1039			MS m/z (M-H) ⁻ 489
1040			MS m/z (M-H) ⁻ 491
1041			MS m/z (M-H) ⁻ 505
1042			MS m/z (M-H) ⁻ 459
1043			MS m/z (M-H) ⁻ 413

Table 2-40



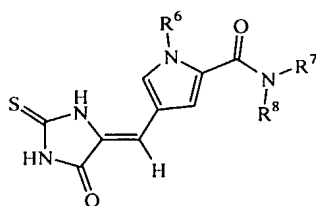
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1044			MS m/z (M-H) ⁻ 420
1045			MS m/z (M-H) ⁻ 472
1046			MS m/z (M-H) ⁻ 475
1047			MS m/z (M-H) ⁻ 544
1048			MS m/z (M-H) ⁻ 404
1049			MS m/z (M-H) ⁻ 434
1050			MS m/z (M-H) ⁻ 446
1051			MS m/z (M-H) ⁻ 484
1052			MS m/z (M-H) ⁻ 486
1053			MS m/z (M-H) ⁻ 500
1054			MS m/z (M-H) ⁻ 454
1055			MS m/z (M-H) ⁻ 408

Table 2-41



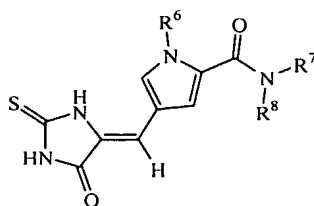
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1056			MS m/z (M-H) ⁺ 425
1057			MS m/z (M-H) ⁺ 525
1058			MS m/z (M-H) ⁺ 426
1059			MS m/z (M-H) ⁺ 457
1060			MS m/z (M-H) ⁺ 455
1061			MS m/z (M-H) ⁺ 505
1062			MS m/z (M-H) ⁺ 499
1063			MS m/z (M-H) ⁺ 517
1064			MS m/z (M-H) ⁺ 522
1065			MS m/z (M-H) ⁺ 470
1066			MS m/z (M-H) ⁺ 522
1067			MS m/z (M-H) ⁺ 475

Table 2-42



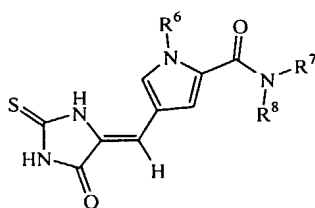
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1068			MS m/z (M-H) ⁺ 409
1069			MS m/z (M-H) ⁺ 509
1070			MS m/z (M-H) ⁺ 410
1071			MS m/z (M-H) ⁺ 441
1072			MS m/z (M-H) ⁺ 439
1073			MS m/z (M-H) ⁺ 489
1074			MS m/z (M-H) ⁺ 483
1075			MS m/z (M-H) ⁺ 501
1076			MS m/z (M-H) ⁺ 506
1077			MS m/z (M-H) ⁺ 454
1078			MS m/z (M-H) ⁺ 506
1079			MS m/z (M-H) ⁺ 459

Table 2-43



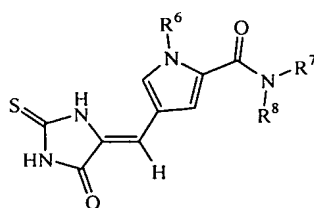
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1080			MS m/z (M-H) ⁻ 449
1081			MS m/z (M-H) ⁻ 549
1082			MS m/z (M-H) ⁻ 450
1083			MS m/z (M-H) ⁻ 481
1084			MS m/z (M-H) ⁻ 479
1085			MS m/z (M-H) ⁻ 529
1086			MS m/z (M-H) ⁻ 523
1087			MS m/z (M-H) ⁻ 541
1088			MS m/z (M-H) ⁻ 546
1089			MS m/z (M-H) ⁻ 494
1090			MS m/z (M-H) ⁻ 546
1091			MS m/z (M-H) ⁻ 499

Table 2-44



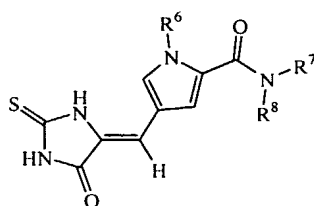
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1092			MS m/z (M-H) ⁻ 469
1093			MS m/z (M-H) ⁻ 569
1094			MS m/z (M-H) ⁻ 470
1095			MS m/z (M-H) ⁻ 501
1096			MS m/z (M-H) ⁻ 499
1097			MS m/z (M-H) ⁻ 549
1098			MS m/z (M-H) ⁻ 543
1099			MS m/z (M-H) ⁻ 561
1100			MS m/z (M-H) ⁻ 566
1101			MS m/z (M-H) ⁻ 514
1102			MS m/z (M-H) ⁻ 566
1103			MS m/z (M-H) ⁻ 519

Table 2-45



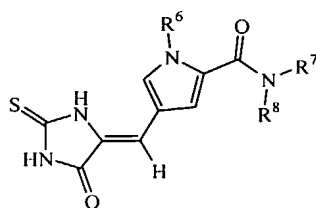
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1104			MS m/z (M-H) ⁺ 405
1105			MS m/z (M-H) ⁺ 505
1106			MS m/z (M-H) ⁺ 406
1107			MS m/z (M-H) ⁺ 437
1108			MS m/z (M-H) ⁺ 435
1109			MS m/z (M-H) ⁺ 485
1110			MS m/z (M-H) ⁺ 479
1111			MS m/z (M-H) ⁺ 497
1112			MS m/z (M-H) ⁺ 502
1113			MS m/z (M-H) ⁺ 450
1114			MS m/z (M-H) ⁺ 502
1115			MS m/z (M-H) ⁺ 455

Table 2-46



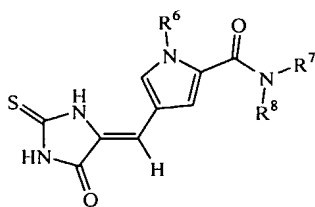
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1116			MS m/z (M-H) ⁺ 459
1117			MS m/z (M-H) ⁺ 559
1118			MS m/z (M-H) ⁺ 460
1119			MS m/z (M-H) ⁺ 491
1120			MS m/z (M-H) ⁺ 489
1121			MS m/z (M-H) ⁺ 539
1122			MS m/z (M-H) ⁺ 533
1123			MS m/z (M-H) ⁺ 551
1124			MS m/z (M-H) ⁺ 556
1125			MS m/z (M-H) ⁺ 504
1126			MS m/z (M-H) ⁺ 556
1127			MS m/z (M-H) ⁺ 509

Table 2-47



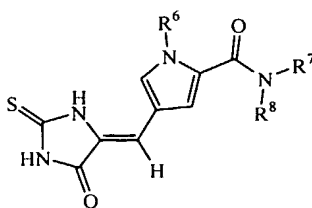
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1128			MS m/z (M-H) ⁺ 421
1129			MS m/z (M-H) ⁺ 521
1130			MS m/z (M-H) ⁺ 422
1131			MS m/z (M-H) ⁺ 453
1132			MS m/z (M-H) ⁺ 451
1133			MS m/z (M-H) ⁺ 501
1134			MS m/z (M-H) ⁺ 495
1135			MS m/z (M-H) ⁺ 513
1136			MS m/z (M-H) ⁺ 518
1137			MS m/z (M-H) ⁺ 466
1138			MS m/z (M-H) ⁺ 518
1139			MS m/z (M-H) ⁺ 471

Table 2-48



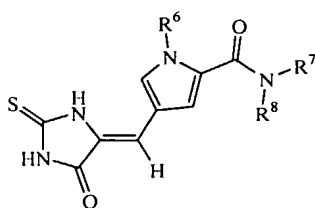
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1140			MS m/z (M-H) ⁺ 416
1141			MS m/z (M-H) ⁺ 516
1142			MS m/z (M-H) ⁺ 417
1143			MS m/z (M-H) ⁺ 448
1144			MS m/z (M-H) ⁺ 446
1145			MS m/z (M-H) ⁺ 496
1146			MS m/z (M-H) ⁺ 490
1147			MS m/z (M-H) ⁺ 508
1148			MS m/z (M-H) ⁺ 513
1149			MS m/z (M-H) ⁺ 461
1150			MS m/z (M-H) ⁺ 513
1151			MS m/z (M-H) ⁺ 466

Table 2-49



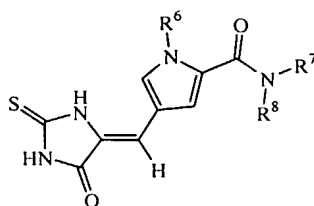
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1152		$\text{—N—(CH}_2\text{)}_2\text{CH}_3$	MS m/z (M-H) ⁺ 395
1153		$\text{—N—(CH}_2\text{)}_2\text{—CH(CH}_3\text{)}_2$	MS m/z (M-H) ⁺ 423
1154		$\text{—N—(CH}_2\text{)}_3\text{OCH}_3$	MS m/z (M-H) ⁺ 425
1155		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 433
1156		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 457
1157		$\text{—N—(CH}_2\text{)}_2\text{—}$	MS m/z (M-H) ⁺ 463
1158		$\text{—N—(CH}_2\text{)}_2\text{—}$	MS m/z (M-H) ⁺ 471
1159		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 477
1160		$\text{—N—(CH}_2\text{)}_2\text{—}$	MS m/z (M-H) ⁺ 487
1161		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 493
1162		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 503
1163		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 511

Table 2-50



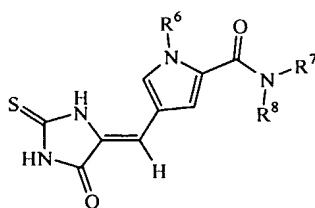
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1164		$\text{—N—(CH}_2\text{)}_2\text{CH}_3$	MS m/z (M-H) ⁺ 427
1165		$\text{—N—(CH}_2\text{)}_2\text{—CH(CH}_3\text{)}_2$	MS m/z (M-H) ⁺ 455
1166		$\text{—N—(CH}_2\text{)}_3\text{OCH}_3$	MS m/z (M-H) ⁺ 457
1167		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 465
1168		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 489
1169		$\text{—N—(CH}_2\text{)}_2\text{—}$	MS m/z (M-H) ⁺ 495
1170		$\text{—N—(CH}_2\text{)}_2\text{—}$	MS m/z (M-H) ⁺ 503
1171		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 509
1172		$\text{—N—(CH}_2\text{)}_2\text{—}$	MS m/z (M-H) ⁺ 519
1173		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 525
1174		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 535
1175		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 543

Table 2-51



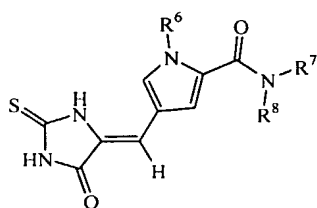
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1176			MS m/z (M-H) ⁺ 451
1177			MS m/z (M-H) ⁺ 479
1178			MS m/z (M-H) ⁺ 481
1179			MS m/z (M-H) ⁺ 489
1180			MS m/z (M-H) ⁺ 513
1181			MS m/z (M-H) ⁺ 519
1182			MS m/z (M-H) ⁺ 527
1183			MS m/z (M-H) ⁺ 533
1184			MS m/z (M-H) ⁺ 543
1185			MS m/z (M-H) ⁺ 549
1186			MS m/z (M-H) ⁺ 559
1187			MS m/z (M-H) ⁺ 567

Table 2-52



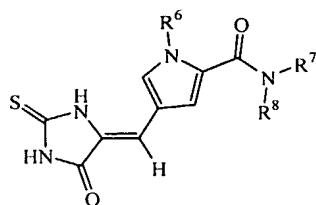
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1188		$\text{—N—(CH}_2\text{)}_2\text{CH}_3$	MS m/z (M-H) ⁺ 463
1189		$\text{—N—(CH}_2\text{)}_2\text{—CH(CH}_3\text{)}_2$	MS m/z (M-H) ⁺ 491
1190		$\text{—N—(CH}_2\text{)}_3\text{OCH}_3$	MS m/z (M-H) ⁺ 493
1191		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 501
1192		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 525
1193		$\text{—N—(CH}_2\text{)}_2\text{—}$	MS m/z (M-H) ⁺ 531
1194		$\text{—N—(CH}_2\text{)}_2\text{—}$	MS m/z (M-H) ⁺ 539
1195		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 545
1196		$\text{—N—(CH}_2\text{)}_2\text{—}$	MS m/z (M-H) ⁺ 555
1197		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 561
1198		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 571
1199		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 579

Table 2-53



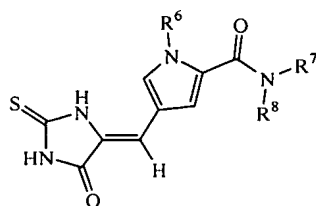
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1200			MS m/z (M-H) ⁻ 399
1201			MS m/z (M-H) ⁻ 427
1202			MS m/z (M-H) ⁻ 429
1203			MS m/z (M-H) ⁻ 437
1204			MS m/z (M-H) ⁻ 461
1205			MS m/z (M-H) ⁻ 467
1206			MS m/z (M-H) ⁻ 475
1207			MS m/z (M-H) ⁻ 481
1208			MS m/z (M-H) ⁻ 491
1209			MS m/z (M-H) ⁻ 497
1210			MS m/z (M-H) ⁻ 507
1211			MS m/z (M-H) ⁻ 515

Table 2-54



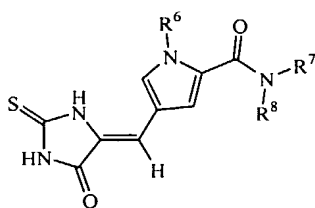
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1212		$\text{—N—(CH}_2\text{)}_2\text{CH}_3$	MS m/z (M-H) ⁺ 403
1213		$\text{—N—(CH}_2\text{)}_2\text{—CH(CH}_3\text{)}_2$	MS m/z (M-H) ⁺ 431
1214		$\text{—N—(CH}_2\text{)}_3\text{OCH}_3$	MS m/z (M-H) ⁺ 433
1215		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 441
1216		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 465
1217		$\text{—N—(CH}_2\text{)}_2\text{—}$	MS m/z (M-H) ⁺ 471
1218		$\text{—N—(CH}_2\text{)}_2\text{—}$	MS m/z (M-H) ⁺ 479
1219		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 485
1220		$\text{—N—(CH}_2\text{)}_2\text{—}$	MS m/z (M-H) ⁺ 495
1221		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 501
1222		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 511
1223		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 519

Table 2-55



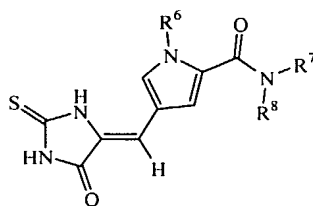
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1224			MS m/z (M-H) ⁺ 419
1225			MS m/z (M-H) ⁺ 447
1226			MS m/z (M-H) ⁺ 449
1227			MS m/z (M-H) ⁺ 457
1228			MS m/z (M-H) ⁺ 481
1229			MS m/z (M-H) ⁺ 487
1230			MS m/z (M-H) ⁺ 495
1231			MS m/z (M-H) ⁺ 501
1232			MS m/z (M-H) ⁺ 511
1233			MS m/z (M-H) ⁺ 517
1234			MS m/z (M-H) ⁺ 527
1235			MS m/z (M-H) ⁺ 535

Table 2-56



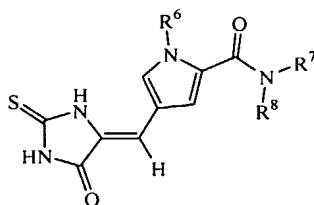
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1236		$\text{—N—(CH}_2\text{)}_2\text{CH}_3$	MS m/z (M-H) ⁺ 443
1237		$\text{—N—(CH}_2\text{)}_2\text{—CH(CH}_3\text{)}_2$	MS m/z (M-H) ⁺ 471
1238		$\text{—N—(CH}_2\text{)}_3\text{OCH}_3$	MS m/z (M-H) ⁺ 473
1239		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 481
1240		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 505
1241		$\text{—N—(CH}_2\text{)}_2\text{—}$	MS m/z (M-H) ⁺ 511
1242		$\text{—N—(CH}_2\text{)}_2\text{—}$	MS m/z (M-H) ⁺ 519
1243		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 525
1244		$\text{—N—(CH}_2\text{)}_2\text{—}$	MS m/z (M-H) ⁺ 535
1245		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 541
1246		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 551
1247		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 559

Table 2-57



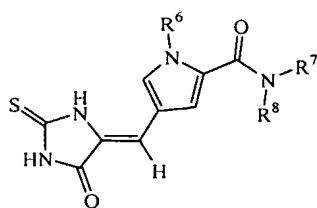
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1248		$\text{—N—CH}_2\text{CH(CH}_3\text{)CH}_2\text{CH}_3$	MS m/z (M-H) ⁺ 423
1249		$\text{—N—(CH}_2\text{)}_2\text{—}$	MS m/z (M-H) ⁺ 475
1250		$\text{—N—(CH}_2\text{)}_3\text{—N—}$	MS m/z (M-H) ⁺ 478
1251		$\text{—N—(CH}_2\text{)}_2\text{—}$	MS m/z (M-H) ⁺ 547
1252		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 407
1253		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 437
1254		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 449
1255		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 487
1256		$\text{—N—CH}_2\text{CHC(CH}_3\text{)(CH}_2\text{)}_2\text{CHC(CH}_3\text{)}_2$	MS m/z (M-H) ⁺ 489
1257		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 503
1258		$\text{—N—(CH}_2\text{)}_2\text{—}$	MS m/z (M-H) ⁺ 457
1259		$\text{—N—(CH}_2\text{)}_2\text{—OH}$	MS m/z (M-H) ⁺ 411

Table 2-58



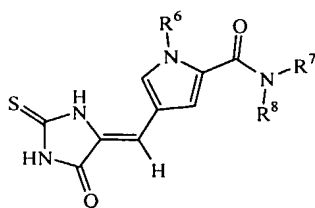
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1260		$\text{—N—CH}_2\text{CH(CH}_3\text{)CH}_2\text{CH}_3$	MS m/z (M-H) ⁺ 455
1261		$\text{—N—(CH}_2\text{)}_2\text{—}$	MS m/z (M-H) ⁺ 507
1262		$\text{—N—(CH}_2\text{)}_3\text{—N—}$	MS m/z (M-H) ⁺ 510
1263		$\text{—N—(CH}_2\text{)}_2\text{—}$	MS m/z (M-H) ⁺ 579
1264		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 439
1265		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 469
1266		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 481
1267		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 519
1268		$\text{—N—CH}_2\text{CHC(CH}_3\text{)(CH}_2\text{)}_2\text{CHC(CH}_3\text{)}_2$	MS m/z (M-H) ⁺ 521
1269		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 535
1270		$\text{—N—(CH}_2\text{)}_2\text{—}$	MS m/z (M-H) ⁺ 489
1271		$\text{—N—(CH}_2\text{)}_2\text{—OH}$	MS m/z (M-H) ⁺ 443

Table 2-59



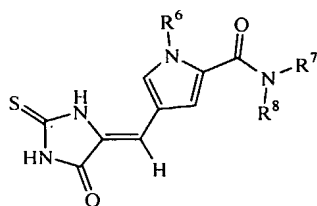
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1272			MS m/z (M-H) ⁻ 479
1273			MS m/z (M-H) ⁻ 531
1274			MS m/z (M-H) ⁻ 534
1275			MS m/z (M-H) ⁻ 603
1276			MS m/z (M-H) ⁻ 465
1277			MS m/z (M-H) ⁻ 493
1278			MS m/z (M-H) ⁻ 505
1279			MS m/z (M-H) ⁻ 543
1280			MS m/z (M-H) ⁻ 545
1281			MS m/z (M-H) ⁻ 559
1282			MS m/z (M-H) ⁻ 513
1283			MS m/z (M-H) ⁻ 467

Table 2-60



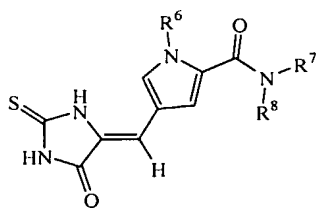
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1284			MS m/z (M-H) ⁺ 491
1285			MS m/z (M-H) ⁺ 543
1286			MS m/z (M-H) ⁺ 546
1287			MS m/z (M-H) ⁺ 615
1288			MS m/z (M-H) ⁺ 475
1289			MS m/z (M-H) ⁺ 505
1290			MS m/z (M-H) ⁺ 517
1291			MS m/z (M-H) ⁺ 555
1292			MS m/z (M-H) ⁺ 557
1293			MS m/z (M-H) ⁺ 571
1294			MS m/z (M-H) ⁺ 525
1295			MS m/z (M-H) ⁺ 479

Table 2-61



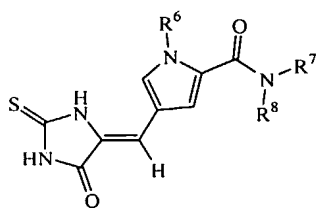
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1296			MS m/z (M-H) ⁻ 427
1297			MS m/z (M-H) ⁻ 479
1298			MS m/z (M-H) ⁻ 482
1299			MS m/z (M-H) ⁻ 551
1300			MS m/z (M-H) ⁻ 411
1301			MS m/z (M-H) ⁻ 441
1302			MS m/z (M-H) ⁻ 453
1303			MS m/z (M-H) ⁻ 491
1304			MS m/z (M-H) ⁻ 493
1305			MS m/z (M-H) ⁻ 507
1306			MS m/z (M-H) ⁻ 461
1307			MS m/z (M-H) ⁻ 415

Table 2-62



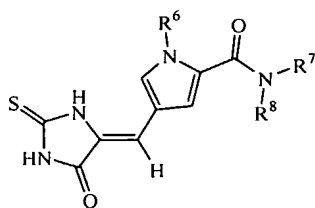
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1308		$\text{—N—CH}_2\text{CH(CH}_3\text{)CH}_2\text{CH}_3$	MS m/z (M-H) ⁺ 431
1309		$\text{—N—(CH}_2\text{)}_2\text{—}$	MS m/z (M-H) ⁺ 483
1310		$\text{—N—(CH}_2\text{)}_3\text{—N—}$	MS m/z (M-H) ⁺ 486
1311		$\text{—N—(CH}_2\text{)}_2\text{—}$	MS m/z (M-H) ⁺ 555
1312		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 415
1313		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 445
1314		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 457
1315		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 495
1316		$\text{—N—CH}_2\text{CHC(CH}_3\text{)(CH}_2\text{)}_2\text{CHC(CH}_3\text{)}_2$	MS m/z (M-H) ⁺ 497
1317		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 511
1318		$\text{—N—(CH}_2\text{)}_2\text{—}$	MS m/z (M-H) ⁺ 465
1319		$\text{—N—(CH}_2\text{)}_2\text{—OH}$	MS m/z (M-H) ⁺ 419

Table 2-63



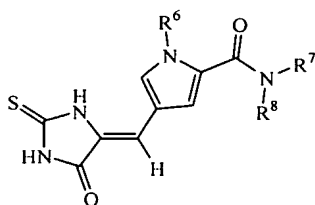
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1320			MS m/z (M-H) ⁻ 447
1321			MS m/z (M-H) ⁻ 499
1322			MS m/z (M-H) ⁻ 502
1323			MS m/z (M-H) ⁻ 571
1324			MS m/z (M-H) ⁻ 431
1325			MS m/z (M-H) ⁻ 461
1326			MS m/z (M-H) ⁻ 473
1327			MS m/z (M-H) ⁻ 511
1328			MS m/z (M-H) ⁻ 513
1329			MS m/z (M-H) ⁻ 527
1330			MS m/z (M-H) ⁻ 481
1331			MS m/z (M-H) ⁻ 435

Table 2-64



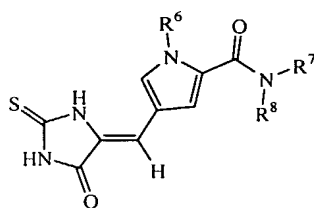
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1332		$\text{—N—CH}_2\text{CH(CH}_3\text{)CH}_2\text{CH}_3$	MS m/z (M-H) ⁺ 471
1333		$\text{—N—(CH}_2\text{)}_2\text{—}$	MS m/z (M-H) ⁺ 523
1334		$\text{—N—(CH}_2\text{)}_3\text{—N—}$	MS m/z (M-H) ⁺ 526
1335		$\text{—N—(CH}_2\text{)}_2\text{—}$	MS m/z (M-H) ⁺ 595
1336		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 455
1337		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 485
1338		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 497
1339		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 535
1340		$\text{—N—CH}_2\text{CHC(CH}_3\text{)(CH}_2\text{)}_2\text{CHC(CH}_3\text{)}_2$	MS m/z (M-H) ⁺ 537
1341		$\text{—N—CH}_2\text{—}$	MS m/z (M-H) ⁺ 551
1342		$\text{—N—(CH}_2\text{)}_2\text{—}$	MS m/z (M-H) ⁺ 505
1343		$\text{—N—(CH}_2\text{)}_2\text{—OH}$	MS m/z (M-H) ⁺ 459

Table 2-65



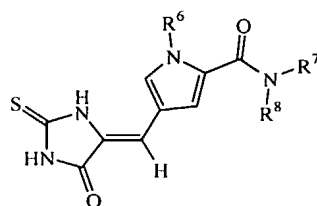
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1344			MS m/z (M-H) ⁻ 419
1345			MS m/z (M-H) ⁻ 519
1346			MS m/z (M-H) ⁻ 420
1347			MS m/z (M-H) ⁻ 451
1348			MS m/z (M-H) ⁻ 449
1349			MS m/z (M-H) ⁻ 499
1350			MS m/z (M-H) ⁻ 493
1351			MS m/z (M-H) ⁻ 511
1352			MS m/z (M-H) ⁻ 516
1353			MS m/z (M-H) ⁻ 464
1354			MS m/z (M-H) ⁻ 516
1355			MS m/z (M-H) ⁻ 469

Table 2-66



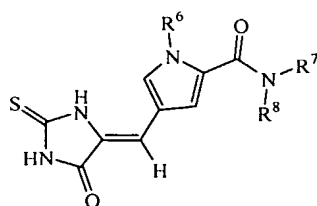
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1356			MS m/z (M-H) ⁺ 451
1357			MS m/z (M-H) ⁺ 551
1358			MS m/z (M-H) ⁺ 452
1359			MS m/z (M-H) ⁺ 483
1360			MS m/z (M-H) ⁺ 481
1361			MS m/z (M-H) ⁺ 531
1362			MS m/z (M-H) ⁺ 525
1363			MS m/z (M-H) ⁺ 543
1364			MS m/z (M-H) ⁺ 548
1365			MS m/z (M-H) ⁺ 496
1366			MS m/z (M-H) ⁺ 548
1367			MS m/z (M-H) ⁺ 501

Table 2-67



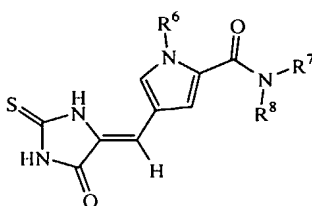
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1368			MS m/z (M-H) ⁺ 475
1369			MS m/z (M-H) ⁺ 575
1370			MS m/z (M-H) ⁺ 476
1371			MS m/z (M-H) ⁺ 507
1372			MS m/z (M-H) ⁺ 505
1373			MS m/z (M-H) ⁺ 555
1374			MS m/z (M-H) ⁺ 549
1375			MS m/z (M-H) ⁺ 567
1376			MS m/z (M-H) ⁺ 572
1377			MS m/z (M-H) ⁺ 520
1378			MS m/z (M-H) ⁺ 572
1379			MS m/z (M-H) ⁺ 525

Table 2-68



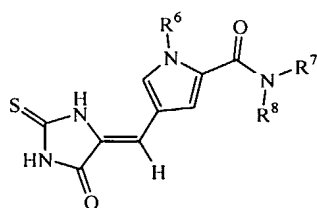
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1380			MS m/z (M-H) ⁺ 487
1381			MS m/z (M-H) ⁺ 587
1382			MS m/z (M-H) ⁺ 488
1383			MS m/z (M-H) ⁺ 519
1384			MS m/z (M-H) ⁺ 517
1385			MS m/z (M-H) ⁺ 567
1386			MS m/z (M-H) ⁺ 561
1387			MS m/z (M-H) ⁺ 579
1388			MS m/z (M-H) ⁺ 584
1389			MS m/z (M-H) ⁺ 532
1390			MS m/z (M-H) ⁺ 584
1391			MS m/z (M-H) ⁺ 537

Table 2-69



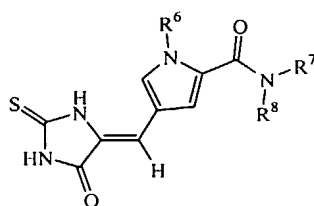
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1392			MS m/z (M-H) ⁻ 423
1393			MS m/z (M-H) ⁻ 523
1394			MS m/z (M-H) ⁻ 424
1395			MS m/z (M-H) ⁻ 455
1396			MS m/z (M-H) ⁻ 453
1367			MS m/z (M-H) ⁻ 503
1398			MS m/z (M-H) ⁻ 497
1399			MS m/z (M-H) ⁻ 515
1400			MS m/z (M-H) ⁻ 520
1401			MS m/z (M-H) ⁻ 468
1402			MS m/z (M-H) ⁻ 520
1403			MS m/z (M-H) ⁻ 473

Table 2-70



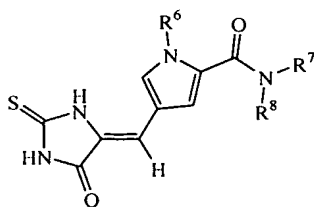
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1404			MS m/z (M-H) ⁺ 427
1405			MS m/z (M-H) ⁺ 527
1406			MS m/z (M-H) ⁺ 428
1407			MS m/z (M-H) ⁺ 459
1408			MS m/z (M-H) ⁺ 457
1409			MS m/z (M-H) ⁺ 507
1410			MS m/z (M-H) ⁺ 501
1411			MS m/z (M-H) ⁺ 519
1412			MS m/z (M-H) ⁺ 524
1413			MS m/z (M-H) ⁺ 472
1414			MS m/z (M-H) ⁺ 524
1415			MS m/z (M-H) ⁺ 477

Table 2-71



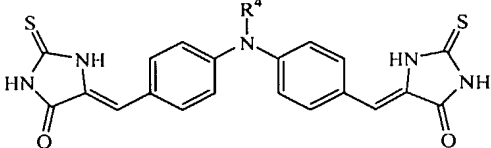
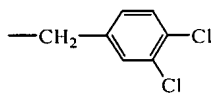
Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1416			MS m/z (M-H) ⁺ 443
1417			MS m/z (M-H) ⁺ 543
1418			MS m/z (M-H) ⁺ 444
1419			MS m/z (M-H) ⁺ 475
1420			MS m/z (M-H) ⁺ 473
1421			MS m/z (M-H) ⁺ 523
1422			MS m/z (M-H) ⁺ 517
1423			MS m/z (M-H) ⁺ 535
1424			MS m/z (M-H) ⁺ 540
1425			MS m/z (M-H) ⁺ 488
1426			MS m/z (M-H) ⁺ 540
1427			MS m/z (M-H) ⁺ 493

Table 2-72



Cpd. No.	R ⁶	NR ⁷ R ⁸	Instrumental Data
1428			MS m/z (M-H) ⁺ 467
1429			MS m/z (M-H) ⁺ 567
1430			MS m/z (M-H) ⁺ 498
1431			MS m/z (M-H) ⁺ 499
1432			MS m/z (M-H) ⁺ 497
1433			MS m/z (M-H) ⁺ 547
1434			MS m/z (M-H) ⁺ 541
1435			MS m/z (M-H) ⁺ 559
1436			MS m/z (M-H) ⁺ 564
1437			MS m/z (M-H) ⁺ 512
1438			MS m/z (M-H) ⁺ 564
1439			MS m/z (M-H) ⁺ 517

Table 3

	
Cpd. No.	R ⁴
1440	

[134] Next, the pharmacological activity of the representative Compound (I) will be described with respect to Test Examples.

Test Example 1: Bio-Tel flush plate assay

- 5 [135] By allowing the addition of repetitions of a telomere sequence (TTAGGG) to a biotinylated telomerase substrate primer, i.e., a reaction catalyzed by telomerase, to occur, telomerase activity was measured. The resultant biotinylated reaction product was captured in a microtiter plate having a streptoavidin coating. By employing a ³³P labeled oligonucleotide probe including a complementary sequence to 3.5 repetitions of the telomere
- 10 sequence, the amount of reaction product associated with telomerase was measured by the following experimental method. The quantification was carried out by, after removing unbound probes through washing, calculating the amount of probes which annealed to the captured telomerase reaction product by scintillation counting.

- [136] In the following method, the respective abbreviations have the following
- 15 meanings.

HCS: hybridization capture solution

SSC: saline sodium citrate (saline containing sodium citrate)

SDS: sodium dodecyl sulfate

DTT: dithiothreitol

- 20 EGTA: ethylenebis(oxyethylenenitrilo)tetraacetic acid

EDTA: ethylenediaminetetraacetic acid

METHOD

- [137] 1) The test compound was dissolved in 100% dimethyl sulfoxide. A solution (2μL) which was obtained by further diluting the above with 50% dimethyl sulfoxide

to a concentration which is 15 times the predetermined level was dispensed in a 96-well microtiter plate.

[138] 2) An enzyme mixture containing telomerase (18 μ L) was added to each test compound solution, which was then pre-incubated at room temperature for 10 minutes to 5 30 minutes.

[139] 3) A reaction associated with telomerase was allowed to begin by adding a master mix (described later)(10 μ L). The plate was sealed and incubated at 37 °C for 90 minutes.

[140] 4) The enzymatic reaction was stopped by adding HCS (15 μ L).

10 [141] 5) The reaction solution (35 μ L) was placed in a 96-well flush plate (NEN) to which streptavidin was allowed to covalently bind. This was incubated at room temperature for 2 hours with slow shaking.

[142] 6) Without incubation, each well was washed four times with the washing solution (2X SSC, 0.1% SDS).

15 [143] 7) The radio activity of the probes which annealed to the biotinylated telomerase reaction product was counted with a scintillation counter.

BUFFER SOLUTION COMPOSITION (MASTER MIX)

50 mM Tris-acetate, pH 8.2

1 mM DTT

20 1 mM EGTA

1 mM magnesium chloride

150 mM potassium acetate

10 μ M dATP

20 μ M dGTP

25 120 μ M dTTP

100 μ M biotinylated primer (5'-biotin-AATCCGTCGAGCAGAGTT-3')

5.4 μ M labeled probe [5'-CCCTAACCCTAACCCTAACCC-(³³P)A₁₋₅₀-3']

1X SSC

saline containing sodium citrate (1X=150mM sodium chloride/15mM trisodium citrate, 30 pH7.2)

HCS

9X SSC, 30mM EDTA, 30mM Tris-HCl, pH7.0

[144] The telomerase reaction inhibition rates of Compound (I) measured by the above method are shown in Table 4.

Table 4

Compound No.	telomerase inhibition rate (% ,3.2 μ mol/L)
5	14
	33
	43
	59
	129
10	167
	168
	210
	229
	233
15	248
	302
	311
	383
	451
20	463
	503
	515
	678
	714
25	726
	751
	961
	1209
	1219
	1345

Test Example 2: In vitro telomerase inhibitory activity

30 [145] The telomerase inhibitory activity of Compound (I) was measured in accordance with a known method (USP No. 5,760,062). Specifically, in the presence of oligodeoxynucleotide, and deoxynucleotide triphosphate serving as substrates, a dimethyl sulfoxide (DMSO) solution of a test compound was mixed with telomerase which was obtained through partial purification of a nucleus extract from HEK293 cells, and the mixture

35 was incubated. The resultant reaction product (DNA having a telomere sequence) was allowed to be adsorbed onto a membrane, and hybridization was effected by using a labeled oligonucleotide probe having a complementary sequence to the telomere sequence. An inhibition rate was calculated from the ratio of the signal intensity of the label on the membrane in the presence of each test compound to the signal intensity of the membrane in

40 the absence of the test compound (control). A compound concentration at which the enzymatic activity was inhibited by 50% relative to the control was defined as IC₅₀. The results of inhibitory activity of Compound (I) are shown in Table 5.

Table 5

Compound No.	Telomerase inhibitory activity (IC ₅₀ ; μ mol/L)
59	2.4
503	3.0
515	8.3

Test Example 3: In vivo telomerase inhibitory activity

[146] After placing a test compound in contact with human kidney carcinoma cell line Caki-1 for 24 hours, a cell extract was prepared by a known method (USP No. 5629154), and the enzymatic activity was measured. Specifically, a cell extract was prepared by using a buffer solution containing 0.5% CHAPS (3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate). By using this extract, a TRAP (Telomeric Repeat Amplification Protocol) assay was performed (manufactured by Intergen, TRAP_{EZE}TM XL Telomerase Detection Kit) in vitro. A ratio (%) of the enzymatic activity value of the extract from cells which were treated with each test compound, to the enzymatic activity value of the extract from cells untreated with the test compound was calculated. In the above method, Compound 59 and Compound 515 according to the present invention inhibited telomerase activity by 50% or more at 30 μ mol/L.

[147] Thus, Compound (I) has an excellent telomerase inhibitory activity, and is useful as a therapeutic agent for diseases associated with telomerase activity, such as malignant tumors.

EXAMPLES

[148] The following examples are offered to illustrate, but not to limit the claimed invention.

[149] Hereinafter, Examples and Reference Examples will be described. The physicochemical data of each compound in the following Examples and Reference Examples were measured by using the following equipment.

¹H NMR: JEOL JNM-EX270 (270 MHz) or JEOL JNM-GX270 (270 MHz)
APCIMS: Micromass LCT

Example 1:

[150] Compound 1 to Compound 575 shown in Table 1 were produced by the following method.

Step (1)

[151] N-(2,4-Dinitrobenzenesulfonyl)glycine ethyl ester (0.1 mL, 1 mol/L tetrahydrofuran solution, 0.1 mmol), triphenylphosphine (0.15 mL, 1 mol/L tetrahydrofuran solution, 0.15 mmol) and a compound represented by R¹OH (0.15 mL, 1 mol/L tetrahydrofuran solution, 0.15 mmol) were added to a 96-well microtiter plate (1.2 mL), and the mixture was stirred at room temperature for 2 to 3 minutes.

[152] Then, diethyl azodicarboxylate (0.15 mL, 1 mol/L tetrahydrofuran solution, 0.15 mmol) was added, and the mixture was sealed and stirred at room temperature for 6 to 24 hours. The resultant reaction solution was concentrated, and thereafter tetrahydrofuran (0.1 mL) and ethyl mercaptoacetate (0.2 mL, 1 mol/L tetrahydrofuran solution, 0.2 mmol) were added, and the mixture was sealed and stirred at room temperature for 16 to 24 hours. After the reaction solution was passed through a BONDESIL SCX column (manufactured by Varian), the contaminants were eluted with a chloroform/methanol-mixed solvent (50% v/v, 2 mL) and methanol (1 mL). Finally, a solution which was eluted with a 4 mol/L hydrogen chloride ethyl acetate solution/methanol-mixed solvent (50% v/v, 1 mL) was concentrated, whereby glycine ethyl ester hydrochloride having substituent R¹ on nitrogen was obtained.

Step (2)

[153] The glycine ethyl ester hydrochloride having substituent R¹ on nitrogen, which was obtained in Step (1), was evenly divided into two aliquots using a 96-well microtiter plate (1.2 mL), to which chloroform (0.4 mL), benzoyl isothiocyanate (0.06 mL, 1 mol/L chloroform solution, 0.06 mmol), and morpholinomethylpolystyrene (0.075 mL, 2% DVB (divinylbenzene), 3.5 mmol/g) were added. This mixture was sealed and stirred at room temperature for 6 to 24 hours. To the reaction solution, chloroform (0.2 mL) and aminomethylated polystyrene (0.075 mL, 1% DVB, about 1.2 mmol/g) were added, and the mixture was sealed and stirred at room temperature for 16 to 24 hours. A residue obtained by filtering and concentrating the resultant reaction solution was dissolved in chloroform (0.8 mL), to which aminomethylated polystyrene (0.15 mL, 1% DVB, about 1.2 mmol/g) was added. This mixture was sealed and stirred at 50°C for 1 to 2 days. By filtering and concentrating the resultant reaction solution, 4-oxo-2-thioxoimidazolidine having substituent R¹ at the 1-position was obtained. If necessary, this compound can be purified by being passed through a BONDESIL SCX column (manufactured by Varian).

Step (3)

[154] To 4-oxo-2-thioxoimidazolidine having R¹ substituent at the 1-position obtained in Step (2), piperidine (0.1 mL, 0.5 mol/L methanol solution, 0.05 mmol) was added, and the mixture was stirred at room temperature for 10 to 15 minutes to achieve

complete dissolution. Then, an arylaldehyde or heteroarylaldehyde (0.1 mL, 0.5 mol/L methanol solution, 0.05 mmol) was added, and the mixture was sealed and stirred at room temperature for 16 to 24 hours. After the resultant reaction solution was concentrated, a single or mixed solvent of ethanol (0.3 mL), chloroform (0.2-0.3 mL), and/or N,N-dimethylformamide (0.2-0.3 mL) was added, depending on the solubility of the compound, to dissolve the compound. To this, AG1-X8 (hydroxide form) resin (0.075-0.15 mL, 1.2 meq/mL) (manufactured by Biorad) was added, and the mixture was sealed and stirred at room temperature for 2 to 24 hours. After removing the supernatant, the resin was washed twice with methanol (0.3 mL). To the resultant resin, a chloroform/methanol-mixed solvent (50% v/v, 0.4 mL) and a 4 mol/L hydrogen chloride ethyl acetate solution (0.05 mL) were added, and the mixture was sealed and stirred at room temperature for 2 to 24 hours. By filtering and concentrating the resultant reaction solution, a 5-arylmethylene-4-oxo-2-thioxoimidazolidine derivative having substituent R¹ at the 1-position or a 5-heteroarylmethylene-4-oxo-2-thioxoimidazolidine derivative having substituent R¹ at the 1-position was obtained with an overall yield of 20 to 40%.

[155] The obtained compounds were identified by mass spectrometry.

[156] The proton nuclear magnetic resonance spectra of representative compounds are shown below.

Compound 59

[01] ¹H NMR (270 MHz, CDCl₃) δ (ppm): 5.34 (s, 2H), 6.34 (s, 1H), 6.9-7.05 (m, 4H), 7.05-7.2 (m, 2H), 7.2-7.45 (m, 6H), 7.5-7.6 (m, 2H), 8.70 (s, 1H).

Compound 229

[158] ¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.4-1.55 (m, 2H), 1.8-2.4 (m, 5H), 3.9-4.1 (m, 2H), 5.4-5.55 and 5.6-5.75 (m, 2H), 6.52 and 6.99 (s, 1H), 7.35-7.45 (m, 3H), 7.9-8.0 (m, 2H), 8.60 and 8.69 (br s, 1H).

Compound 311

[159] ¹H NMR (270 MHz, CDCl₃) δ (ppm): 0.5-0.65 (m, 4H), 1.1-1.25 (m, 1H), 4.04 (d, 2H, J= 6.9 Hz), 6.44 (s, 1H), 7.17 (t, 1H, J= 8.7 Hz), 7.85-7.95 (m, 1H), 8.10 (dd, 1H, J= 6.9, 2.3 Hz), 8.62 (br s, 1H).

Compound 383

[160] ¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.17 (t, 3H, J= 7.0 Hz), 3.48 (q, 2H, J= 7.0 Hz), 3.5-3.6 (m, 2H), 3.6-3.7 (m, 2H), 3.82 (t, 2H, J= 5.1 Hz), 4.30 (t, 2H, J= 5.1 Hz),

6.86 (s, 1H), 7.15 (t, 1H, J= 8.6 Hz), 7.85-7.95 (m, 1H), 8.06 (dd, 1H, J= 7.1, 2.1 Hz), 8.66 (br s, 1H).

Compound 451

[161] ¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.95-2.1 (m, 2H), 2.72 (t, 2H, J= 7.0 Hz), 3.81 (s, 3H), 4.0-4.1 (m, 2H), 6.06 (s, 1H), 6.88 (d, 2H, J= 8.6 Hz), 7.06 (t, 2H, J= 8.7 Hz), 7.16 (d, 2H, J= 8.6 Hz), 7.85-7.95 (m, 2H), 8.58 (br s, 1H).

Compound 463

[162] ¹H NMR (270 MHz, CDCl₃) δ (ppm): 3.68 and 3.85 (s, 6H), 3.78 and 3.84 (s, 3H), 5.14 and 5.28 (s, 2H), 5.84 and 6.54 (s, 2H), 6.42 and 6.87 (s, 1H), 7.0-7.15 and 7.85-7.95 (m, 4H), 8.70 and 8.79 (br s, 1H).

Compound 503

[163] ¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.42 (s, 3H), 3.06 (t, 2H, J= 7.4 Hz), 4.24 (t, 2H, J= 7.4 Hz), 6.12 (s, 1H), 7.13 (t, 1H, J= 8.7 Hz), 7.19 (s, 4H), 7.55-7.65 (m, 1H), 7.87 (dd, 1H, J= 7.1, 2.2 Hz), 8.61 (br s, 1H).

Compound 515

[164] ¹H NMR (270 MHz, CDCl₃) δ (ppm): 0.97 (t, 3H, J= 7.4 Hz), 1.4-1.55 (m, 2H), 1.65-1.8 (m, 2H), 3.95 (t, 2H, J= 6.4 Hz), 5.27 (s, 2H), 6.28 (s, 1H), 6.99 (d, 2H, J= 8.7 Hz), 7.10 (t, 1H, J= 7.1 Hz), 7.22 (d, 2H, J= 8.7 Hz), 7.7-7.8 (m, 1H), 7.93 (dd, 1H, J= 7.1, 2.1 Hz), 8.69 (br s, 1H).

Example 2

[165] Compound 576 to Compound 767, Compound 864 to Compound 1055, Compound 1152 to Compound 1235, and Compound 1248 to Compound 1331 shown in Table 2 were produced by the following method.

[01] 4-Formyl-2-(trichloroacetyl)pyrrole (17 mg, 70 μmol), obtained by a method described in *J. Org. Chem.*, vol. 43, pp. 4849-4853 (1978), was dissolved in N,N-dimethylformamide (0.4 mL), and a compound (100 μmol) represented by R⁷R⁸NH was added. This mixture was stirred at 55 °C for 12 hours. The solvent was removed under reduced pressure. The resulting residue was dissolved in chloroform (0.6 mL), and N-methylisatoic anhydride polystyrene (40 mg, 80 μmol) was added. This mixture was stirred at room temperature for 15 hours. After filtering the reaction mixture, the solvent was distilled off, and the resulting residue was dissolved in N,N-dimethylformamide (0.4 mL). For introducing the substituent R^{6a} upon a nitrogen atom on the pyrrole ring, a corresponding

halogenated benzyl(100 μmol), 2-(tert-butylimino)-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphospholine on polystyrene (45 mg, 99 μmol) was added, and the mixture was stirred at 30 °C for 12 hours. After filtering the reaction mixture, the solvent was distilled off under reduced pressure. The resulting residue was dissolved in chloroform/methanol (10:1)(0.6 mL), and N-(2-mercaptoethyl)aminomethyl-polystyrene (25 mg, 38 μmol) and Biorad[®] AG1-X8OH⁻ resin (90 mg, 180 μmol) were added. This mixture was stirred at room temperature for 12 hours. After filtering the reaction mixture, the solvent was distilled off under reduced pressure. The resulting residue was dissolved in ethanol (0.5 mL). To this, 4-oxo-2-thioxoimidazolidine (3.6 mg, 31 μmol) and piperidine (4.0 μL , 40 μmol) were added, and the mixture was stirred at room temperature for 12 hours. The reaction mixture was allowed to cool down to room temperature, and was diluted with chloroform (0.3 mL), methanol (0.3 mL), and tetrahydrofuran (0.3 mL). To this, Biorad[®] AG1-X8OH⁻ resin (90 mg, 180 μmol) was added, and the mixture was stirred at room temperature for 12 hours. Biorad[®] AG1-X8OH⁻ resin was collected by filtration and suspended in chloroform/methanol (1:1)(1.5 mL), and a 4 mol/L hydrogen chloride ethyl acetate solution (400 μL , 400 μmol) was added. This mixture was stirred at room temperature for 3 hours. After filtering the reaction mixture, the solvent was distilled off under reduced pressure, whereby the desired compound was obtained.

[167] The resulting compounds were identified by mass spectrometry.

[168] The proton nuclear magnetic resonance spectra and element analytical values of representative Compound 714 are shown below.

Compound 714

[169] ¹H-NMR (270 MHz, DMSO-d₆) δ (ppm): 0.70-0.91 (m, 2H), 1.00-1.23 (m, 3H), 1.29-1.45 (m, 1H), 1.47-1.71 (m, 5H), 2.95 (t, 2H, J = 5.9 Hz), 5.78 (s, 2H), 6.45 (s, 1H), 6.69 (d, 1H, J = 7.6 Hz), 7.34 (s, 1H), 7.41-7.47 (m, 1H), 7.56-7.62 (m, 1H), 7.83 (s, 1H), 7.84 (d, 1H, J = 7.6 Hz), 7.97 (t, 1H, J = 5.9 Hz), 11.55 (s, 1H), 12.21 (s, 1H).

[170] Element analysis: C₂₄H₂₅N₅O₂S

[171] calcd: C, 64.41; H, 5.63; N, 15.65.

[172] found: C, 64.43; H, 5.92; N, 15.59.

Example 3

[173] Compound 768 to compound 863, Compound 1056 to Compound 1151, and Compound 1344 to Compound 1427 shown in Table 2 were produced by the following method.

[174] 4-Formyl-2-(methoxycarbonyl)pyrrole (11 mg, 70 μmol), obtained by a method described in *J. Org. Chem.*, vol. 43, pp. 4849-4853 (1978), was dissolved in N,N-dimethylformamide (0.4 mL). A halogenated benzyl (100 μmol) compound corresponding to R^{6a} and 2-(tert-butylimino)-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphospholine on polystyrene (45 mg, 99 μmol) were added, and the mixture was stirred at 30 °C for 12 hours. After filtering the reaction mixture, the solvent was distilled off under reduced pressure. The resulting residue was dissolved in chloroform/methanol (10:1) (0.6 mL). N-(2-Mercaptoethyl)aminomethyl-polystyrene (25 mg, 38 μmol) and Biorad[®] AG1-X8OH⁻ resin (90 mg, 180 μmol) were added, and the mixture was stirred at room temperature for 12 hours. After filtering the reaction mixture, the solvent was distilled off under reduced pressure. The resulting residue was dissolved in methanol (0.3 mL), and a 1 mol/L aqueous solution of sodium hydroxide (120 μL , 120 μmol) was added. This mixture was stirred at 30 °C for 12 hours. The solvent was distilled off under reduced pressure, and the resulting residue was dissolved in methanol (0.3 mL). A 1 mol/L aqueous solution of hydrochloric acid (130 μL , 130 μmol) was added, and the mixture was stirred at room temperature for 15 minutes. The solvent was distilled off, and the resulting residue was dissolved in chloroform (0.4 mL). To this, 1-hydroxybenzotriazole (8.5 mg, 63 μmol), a compound (100 μmol) represented by $\text{R}^7\text{R}^8\text{NH}$, 1-hydroxybenzotriazole (8.5 mg, 63 μmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide polymer bound (100 mg, 140 μmol) were added, and the mixture was stirred at 55 °C for 12 hours. After filtering the reaction mixture, the solvent was distilled off under reduced pressure, and the resulting residue was dissolved in chloroform (0.6 mL). To this, 4-polyvinylpyridine (23 mg, 219 μmol) and benzoyl chloride polymer bound (23 mg, 48 μmol) were added, and the mixture was stirred at room temperature for 12 hours. After filtering the reaction mixture, the solvent was distilled off, and the resulting residue was dissolved in ethanol (0.5 mL). To this, 4-oxo-2-thioxoimidazolidine (3.6 mg, 31 μmol) and piperidine (4.0 μL , 40 μmol) were added, and the mixture was stirred at room temperature for 12 hours. The reaction mixture was allowed to cool down to room temperature, and was diluted with chloroform (0.3 mL), methanol (0.3 mL), and tetrahydrofuran (0.3 mL). To this, Biorad[®] AG1-X8OH⁻ resin (90 mg, 180 μmol) was added, and the mixture was stirred at room temperature for 12 hours. Biorad[®] AG1-X8OH⁻ resin was collected by filtration and suspended in chloroform/methanol (1:1)(1.5 mL), a solution of hydrogen chloride in ethyl acetate (4 M, 400 μL , 400 μmol) was added, and the mixture was stirred at room temperature for 3 hours. After filtering the reaction mixture, the solvent was distilled off under reduced pressure, whereby the desired compound was obtained.

[175] The resulting compounds were identified by mass spectrometry.

Example 4

[176] Compounds 1236-1247 and 1332-1343 shown in Table 2 were produced by the following method.

5 [01] 1-Diphenylmethyl-4-formyl-2-(trichloroacetyl)pyrrole (28 mg, 70 μ mol), obtained by a method described in Japanese Laid-Open Publication No. 11-209344, was dissolved in N,N-dimethylformamide (0.4 mL), and a compound (100 μ mol) represented by R^7R^8NH was added. This mixture was stirred at 55 °C for 12 hours. The solvent was distilled off under reduced pressure, and the resulting residue was dissolved in chloroform
10 (0.6 mL). To this, N-methylisatoic anhydride polystyrene (40 mg, 80 μ mol) was added, and the mixture was stirred at room temperature for 15 hours. After filtering the reaction mixture, the solvent was distilled off, and the resulting residue was dissolved in ethanol (0.5 mL). To this, 4-oxo-2-thioxoimidazolidine (3.6 mg, 31 μ mol) and piperidine (4.0 μ L, 40 μ mol) were added, and the mixture was stirred at room temperature for 12 hours. The reaction mixture
15 was allowed to cool down to room temperature, and was diluted with chloroform (0.3 mL), methanol (0.3 mL), and tetrahydrofuran (0.3 mL). To this, Biorad[®] AG1-X8OH⁻ resin (90 mg, 180 μ mol) was added, and the mixture was stirred at room temperature for 12 hours. Biorad[®] AG1-X8OH⁻ was collected by filtration and suspended in chloroform/methanol (1:1)(1.5 mL), and a solution of hydrogen chloride in ethyl acetate (4 M, 400 μ L, 400 μ mol)
20 was added. This mixture was stirred at room temperature for 3 hours. After filtering the reaction mixture, the solvent was distilled off under reduced pressure, whereby the desired compound was obtained.

[178] The resulting compounds were identified by mass spectrometry.

Example 5

25 [179] Compounds 1428-1439 shown in Table 2 were produced by the following method.

[01] 1-Diphenylmethyl-4-formyl-2-(trichloroacetyl)-pyrrole (28 mg, 70 μ mol), obtained by a method described in Japanese Laid-Open Publication No. 11-209344, was dissolved in methanol (0.4 mL), and a 28% sodium methoxide methanol solution (27 μ L, 140
30 μ mol) was added. This mixture was stirred at room temperature for 12 hours. The reaction mixture was diluted with ethyl acetate, and sequentially washed with water and brine. After drying the organic layer over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The resulting residue was dissolved in methanol (0.3 mL), and a 1

mol/L aqueous solution of sodium hydroxide (120 μ L, 120 μ mol) was added. This mixture was stirred at 30 °C for 12 hours. The solvent was distilled off under reduced pressure, and the resulting residue was dissolved in methanol (0.3 mL). To this, a 1 mol/L aqueous solution of hydrochloric acid (130 μ L, 130 μ mol) was added, and the mixture was stirred at room temperature for 15 minutes. The solvent was distilled off, and the resulting residue was dissolved in chloroform (0.4 mL). To this, 1-hydroxybenzotriazole (8.5 mg, 63 μ mol), a compound (100 μ mol) represented by R⁷R⁸NH, 1-hydroxybenzotriazole (8.5 mg, 63 μ mol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide polymer bound (100 mg, 140 μ mol) were added. This mixture was stirred at 55 °C for 12 hours. After filtering the reaction mixture, the solvent was distilled off under reduced pressure, and the resulting residue was dissolved in chloroform (0.6 mL). To this, 4-polyvinylpyridine (23 mg, 219 μ mol) and benzoyl chloride polymer bound (23 mg, 48 μ mol) were added, and the mixture was stirred at room temperature for 12 hours. After filtering the reaction mixture, the solvent was distilled off, and the resulting residue was dissolved in ethanol (0.5 mL). To this, 4-oxo-2-thioxoimidazolidine (3.6 mg, 31 μ mol) and piperidine (4.0 μ L, 40 μ mol) were added, and the mixture was stirred at room temperature for 12 hours. The reaction mixture was allowed to cool down to room temperature, and was diluted with chloroform (0.3 mL), methanol (0.3 mL), and tetrahydrofuran (0.3 mL). To this, Biorad[®] AG1-X8OH⁻ resin (90 mg, 180 μ mol) was added, and the mixture was stirred at room temperature for 12 hours. Biorad[®] AG1-X8OH⁻ resin was collected by filtration and suspended in chloroform/methanol (1:1) (1.5 mL), and a solution of hydrogen chloride in ethyl acetate (4 M, 400 μ L, 400 μ mol) was added. This mixture was stirred at room temperature for 3 hours. After filtering the reaction mixture, the solvent was distilled off under reduced pressure, whereby the desired compound was obtained.

[181] The obtained compounds were identified by mass spectrometry.

Example 6: (Compound 1440)

[182] N-(3,4-Dichlorobenzyl)-4',4''-diformyldiphenylamine (69 mg, 0.18 mmol) obtained in Reference Example 3 was dissolved in ethanol (10 mL). To this, thiohydantoin (83 mg, 0.72 mmol) and lithium hydroxide (43 mg, 1.8 mmol) were added, and the mixture was stirred for 15 minutes while refluxing under heat. Water (30 mL) was added to the reaction mixture, and the reaction mixture was adjusted to pH 3 with 1 mol/L hydrochloric acid. The precipitated crystals were collected by filtration. Trituration was performed with methanol, whereby Compound 1440 (68 mg, yield: 65%) was obtained.

[183] ^1H NMR (270 MHz, DMSO- d_6) δ (ppm): 5.17 (s, 2H), 6.44 (s, 2H), 7.14 (d, 4H, $J = 8.9$ Hz), 7.29 (dd, 1H, $J = 2.0, 8.3$ Hz), 7.56 (d, 1H, $J = 2.0$ Hz), 7.59 (d, 1H, $J = 8.3$ Hz), 7.69 (d, 4H, $J = 8.9$ Hz), 12.04 (br s, 2H), 12.29 (br s, 2H).

Reference Example 1: N-(tert-Butoxycarbonyl)-4,4'-diformyldiphenylamine

5 Step (1)

[184] Bis(4-bromophenyl)amine (2.13 g, 6.51 mmol) was dissolved in tetrahydrofuran (100 mL), and di-tert-butyl dicarbonate (3.00 mL, 13.1 mmol) was added. After stirring at room temperature for 8 hours, this mixture was refluxed for 4 hours. Next, 4-dimethylaminopyridine (1.70 g, 13.9 mmol) was added, and the mixture was refluxed for 4
10 more hours. The reaction mixture was allowed to cool down to room temperature. To this, a saturated aqueous solution of sodium bicarbonate was added, and extraction was carried out with chloroform. The organic layer was washed with brine, and dried over anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, purification was carried out by silica gel column chromatography (chloroform), whereby N-(tert-
15 butoxycarbonyl)-4,4'-dibromodiphenylamine (2.50 g, 99%) was obtained.

[185] ^1H NMR (270MHz, CDCl_3) δ (ppm) 1.44 (s, 9H), 7.06 (d, 4H, $J = 8.9$ Hz), 7.42 (d, 4H, $J = 8.9$ Hz).

Step (2)

[186] The aforementioned compound (1.47 g, 3.46 mmol) was dissolved in
20 tetrahydrofuran (20 mL), and the mixture was cooled to -78°C . Next, n-butyl lithium (1.50 mol/L hexane solution; 6.0 mL, 9.0mmol) was added, and the mixture was stirred for 40 minutes. Thereafter, N,N-dimethylformamide (1.10 mL, 14.3 mmol) was added, and the mixture was stirred for additional 30 more minutes. Next, the mixture was warmed to room temperature, and stirred for 8 hours. A saturated aqueous solution of ammonium chloride
25 was added to the reaction mixture, and extraction was carried out with chloroform. The organic layer was washed with brine, and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and purification was carried out by silica gel column chromatography (20:1 - 6:1 - 3:1 - 2:1 hexane/ethyl acetate), whereby the aforementioned compound (739 mg, 79%) was obtained.

30 [187] ^1H NMR (270 MHz, CDCl_3) δ (ppm): 1.47 (s, 9H), 7.35 (d, 4H, $J = 8.4$ Hz), 7.86 (d, 4H, $J = 8.4$ Hz), 9.98 (s, 2H).

Reference Example 2: 4,4'-Diformyldiphenylamine

[188] N-(tert-butoxycarbonyl)-4,4'-diformyldiphenylamine (2.33 g, 7.16 mmol) obtained from Reference Example 1 was dissolved in dichloromethane (20 mL). To this, trifluoroacetic acid (10 mL) was added at room temperature, and the mixture was stirred at
5 the same temperature for 1.5 hours. To the reaction mixture, a 6 mol/L aqueous solution of sodium hydroxide was added, and extraction was carried out with chloroform. The organic layer was washed with brine, and dried using anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. Trituration was performed with methanol, whereby the aforementioned compound (1.18 g, 73%) was obtained.

10 [189] ¹H NMR (270 MHz, CDCl₃) δ (ppm): 6.51 (br s, 1H), 7.25 (d, 4H, J = 8.6 Hz), 7.86 (d, 4H, J = 8.6 Hz), 9.89 (s, 2H).

Reference Example 3: N-(3,4-Dichlorobenzyl)-4',4''-diformyldiphenylamine

[190] 4,4'-Diformyldiphenylamine (404 mg, 1.79 mmol) obtained in Reference Example 2 was dissolved in tetrahydrofuran (20 mL). To this, sodium hydride (60% in
15 mineral oil dispersion, 153 mg, 3.83 mmol) was added, and the mixture was stirred at room temperature for 10 minutes. Next, 3,4-dichlorobenzyl bromide (1.18 g, 4.92 mmol) was added, and the mixture was stirred at room temperature for 2 hours. Water was added to the reaction mixture. After extraction was carried out with chloroform, the organic layer was washed with brine, and dried over anhydrous sodium sulfate. The solvent was distilled off
20 under reduced pressure. Purification was carried out by silica gel column chromatography (4:1 - 2:1 hexane/ethyl acetate), whereby the aforementioned compound (614 mg, 89%) was obtained.

[01] ¹H NMR (270 MHz, CDCl₃) δ (ppm): 5.09 (s, 2H), 7.12 (dd, 1H, J = 2.0, 8.2 Hz), 7.21 (d, 4H, J = 8.9 Hz), 7.37 (d, 1H, J = 2.0 Hz), 7.40 (d, 1H, J = 8.2 Hz), 7.82 (d, 4H, J
25 = 8.9 Hz), 9.89 (s, 2H).

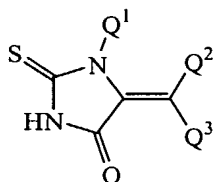
[192] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent
30 applications cited herein are hereby incorporated by reference in their entirety for all purposes.

WHAT IS CLAIMED IS:

1. A telomerase inhibitor comprising as an active ingredient a compound having a 4-oxo-2-thioxoimidazolidine skeleton and having telomerase inhibitory activity.

2. An antitumor agent comprising as an active ingredient a compound having a 4-oxo-2-thioxoimidazolidine skeleton and having telomerase inhibitory activity.

3. A telomerase inhibitor comprising a compound of the formula:



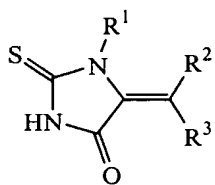
(I)

or a pharmaceutically acceptable salt thereof,
wherein

Q¹ is hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted arylalkenyl, substituted or unsubstituted heteroarylalkenyl, substituted or unsubstituted arylalkynyl, substituted or unsubstituted heteroarylalkynyl, substituted or unsubstituted lower alkanoyl, substituted or unsubstituted lower alkenoyl, substituted or unsubstituted lower alkynoyl, substituted or unsubstituted arylalkanoyl, substituted or unsubstituted heteroarylalkanoyl, substituted or unsubstituted arylalkenoyl, substituted or unsubstituted heteroarylalkenoyl, substituted or unsubstituted arylalkynoyl, or substituted or unsubstituted heteroarylalkynoyl; one of Q² and Q³ is hydrogen, and the other is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

4. An antitumor agent comprising the compound according to claim 3 or a pharmaceutically acceptable salt thereof, as an active ingredient.

5. A compound of the formula:



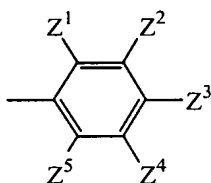
(Ia)

or a pharmaceutically acceptable salt thereof,

wherein

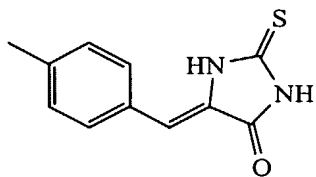
R¹ is hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted arylalkenyl, substituted or unsubstituted heteroarylalkenyl, substituted or unsubstituted arylalkynyl, or substituted or unsubstituted heteroarylalkynyl;

one of R² and R³ is hydrogen, and the other is



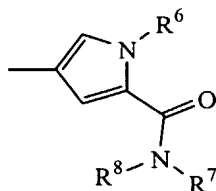
[wherein

Z¹ to Z⁵ are the same or different, and each represents hydrogen, substituted or unsubstituted lower alkyl, unsubstituted lower alkoxy having no asymmetric carbon atom, substituted lower alkoxy, unsubstituted lower alkylthio having no asymmetric carbon atom, substituted lower alkylthio, NR⁴R⁵ (wherein each of R⁴ and R⁵ is independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, lower alkanoyl, aroyl, heteroaroyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroarylalkyl, or



or R⁴ and R⁵ together with the nitrogen atom to which they are attached to form a substituted or unsubstituted heterocyclic group), nitro, cyano, aryl, heteroaryl, aryloxy, heteroaryloxy, aralkyloxy, heteroarylalkyloxy or halogen, or

two of adjacent Z¹ to Z⁵ on the benzene ring together form a moiety of the formula -O-(CH₂)_n-O- (wherein n is an integer of 1 or 2)], substituted or unsubstituted naphthyl, substituted or unsubstituted heteroaryl, or

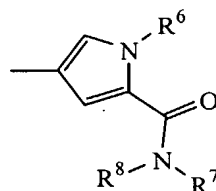


(wherein

R⁶ has the same meaning as the aforementioned R¹;

each of R⁷ and R⁸ is independently hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroarylalkyl, or R⁷ and R⁸ together with the nitrogen atom to which they are attached to form a substituted or unsubstituted heterocyclic group);

with the proviso that when one of R² and R³ is hydrogen, and the other is not



(wherein

R⁶, R⁷ and R⁸ have the same meanings as defined above, respectively), R¹ represents the above-mentioned substituent other than hydrogen and substituted or unsubstituted methyl.

6. A telomerase inhibitor comprising the compound according to claim 5 or a pharmaceutically acceptable salt thereof, as an active ingredient.

7. An antitumor agent comprising the compound according to claim 5 or a pharmaceutically acceptable salt thereof, as an active ingredient.

8. A pharmaceutical composition comprising the compound according to claim 5 or a pharmaceutically acceptable salt thereof, as an active ingredient.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/50042

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/341, 389; 546/274.4; 548/311.1, 311.7, 314.7, 315.1, 316.1, 317.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,649,145 A (ROSS ET AL.) 10 March 1987 (10/03/87), see entire document, especially compounds 14, 15, etc. in columns 9 and 10.	3-8
X	US 5,464,856 A (CETENKO ET AL.) 07 November 1995 (07/11/95), see entire document, especially compounds 85, 86, etc. in columns 21 and 22.	3-8
X	US 5,614,541 A (BACKSTROM ET AL.) 25 March 1997 (25/03/97), see entire document, especially Example 1 in column 7.	3-8

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

25 MARCH 2002

Date of mailing of the international search report

08 MAY 2002

 Name and mailing address of the ISA/US
 Commissioner of Patents and Trademarks
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Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/50042

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chem. abstr., Vol. 126, No.8, 24 February 1997 (Columbus, OH, USA), page 19, column 1, the abstract No. 98856, AL-OBAID ET AL. '5-Substituted-2-thiohydantoin analogs as a novel class of antitumor agents.' Anti-Cancer Drugs. 1996, 7(8), pages 873-880 (Eng).	3-8
X	Chem. abstr., Vol. 113, No. 6, 07 August 2000 (Columbus, OH, USA), page 692, column 2, the abstract No. 73977y, KHODAIR ET AL. 'Synthesis, conformational analysis and antitumor testing of 5-(Z)-arylidene-4-imidazolidinone derivatives.' Phosphorus, Sulfur and Silicon and the Related Elements. 1998, 140, pages 159-181 (Eng).	3-8

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/50042

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1 AND 2
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

the claims cannot be searched because the products are not adequately defined.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/50042

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (7):

A61K 31/4178, 31/4166, 31/4439; C07D 233/86, 401/06, 403/06, 405/06, 409/06

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

514/341, 389; 546/274.4; 548/311.1, 311.7, 314.7, 315.1, 316.1, 317.1